Biological Factors in Chronic PTSD

Thesis submitted for the degree of
Doctor of Philosophy

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Abstract

This is a prospective study of a cohort sample of injured Kuwaiti First Gulf War survivors designed to investigate the prevalence of psychiatric morbidity due to combat and exposures to traumatic events. The study included two main phases. The first phase conducted in 1998, and in 2003 the second phase was executed. This study was designed to investigate the contribution of combat physical injury to the neurobiology of posttraumatic stress disorder (PTSD), prevalence rates of PTSD, depression, anxiety and other psychological morbidity, and predictors of chronic PTSD.

The first assessment was in 1998 and the second assessment in 2003 that involved biological investigations. Beside the clinical interview and the physical examination of the site of injury, multiple psychological scales and questionnaires were used.

Based on DSM-IV criteria of PTSD, after the second assessment the population of this study were classified to: Chronic PTSD (have PTSD at both assessments), Delayed PTSD (have PTSD only on the second assessment), Recovered (have PTSD only in the first assessment), and Never PTSD (have no PTSD in both assessments). The biological assessment include: blood investigations, BMI, and visual analogue. The data of the study were analyzed based on the four PTSD subgroups.

In the first chapter an introduction to the First Gulf War was presented followed by the second chapter that discussed literature review. The third chapter tackled the methods used in this study. The fourth to the sixth chapters discussed the results of this study regarding prevalence of Chronic PTSD, Cortisol and PTSD and Thyroid hormones and PTSD respectively. The last chapter presented the limitations and strengths of the study

There were three main hypotheses. First: combat injured survivors with chronic PTSD have cluster of symptoms severity similar to delayed PTSD after 13 years of the trauma and the prevalence of chronic PTSD is constant over time. Second: low cortisol levels observed in chronic PTSD are constant with chronicity, normalize with recovery, unrelated to degree of disability, and are influenced by comorbid disorders. Third: there is minor role for thyroid hormones in chronic PTSD.

All of registered Kuwaiti combat injured survivors at the Social Development Office in Kuwait, were approached to voluntary participate in this study. Of 234 individuals 212 participate in the first stage, and out of these 123 participate in the second stage with the addition of 33 new cases that were not examined in 1998 but were registered in SDO after 1998. An informed consent was taken from the participants at both phases.

The participants were assessed using General Health Questionnaire, Trauma Questionnaire, Clinician Administered PTSD Scale, Eysenck Personality Questionnaire, Symptom Checklist-90 Revised, and Life Event Scale. Questionnaires and scales applied in the first stage were applied in the second stage with the addition of Impact of Event Scale, Composite International Diagnostic Interview and Scale of Gulf War Syndrome.

Biochemical assessment comprised cortisol level, thyroxine (fT4), free triiodothyronine (fT3) and thyroid stimulating hormone (TSH). The blood samples were taken before starting the interview. Physical assessment involved measurements of: pulse rate, systolic and diastolic blood pressure, waist-hip circumference, body mass index and visual analogue before and after the interview.

Data entry program using Statistical Package for Social Scientists was used to enter data and analysis.

The prevalence rate of delayed onset PTSD (14.6%), chronic PTSD (15.4) recovered from PTSD (22.8%) and never had PTSD (47.2%). With chronic PTSD there are higher cluster of PTSD symptoms severity, not related to severity of physical injury, has more prevalence of PTSD associated symptoms, higher comorbid psychiatric disorders. Intrusions, avoidance and arousal are PTSD cluster of symptoms more predictive of future development of PTSD after the injury. There was a low baseline cortisol level with chronic PTSD, and it was significantly lower in participants with delayed PTSD. Furthermore trauma itself rather than PTSD diagnosis may have an impact on cortisol level. Other psychiatric comorbidity has an enhancing effect on cortisol level.

The levels of thyroid hormones were within the normal range. The trend of thyroid function in delayed and chronic PTSD is lower fT3, and TSH and higher fT4 levels, with higher fT3 levels in delayed PTSD compared to chronic PTSD. It was found that the higher severity of trauma score with PTSD the higher fT3 mean values.

Statement of Originality

I declare that this thesis report is my own work, except where acknowledged. It has not been submitted for academic credit (award of any degree) or diploma) in any University or other tertiary institution, and to the best of my knowledge and belief, contain no material previously published or written by another person, except where due reference has been made in the text.

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Abdullah M. Al-Hammadi

Date:

I believe that this thesis is properly presented, conforms to the specification for the degree of sufficient standard to be, prima facie, worthy of examination.

Professor Alexander Cowell McFarlane

Principal Supervisor

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Chapter I. Introduction and Review of Literature

1. Kuwait and FGW

1. A. Kuwait Background

The State of Kuwait lies on the northeast coast of the Arabian Peninsula, bordered on the east by the Arabian Gulf, in the north by Iraq, and in the west and south by the Kingdom of Saudi Arabia. Its total area is about 18000 square kilometers, and its population is about 1.8 million (According to January 1995 estimate-Public Authority of Civil Information).

1. B. Invasion and Occupation of Kuwait 1990-1991

Kuwait's recorded history goes back to 1716 when the first ruler was appointed, although it has existed since 1613. A foreign force had never occupied Kuwait City before 1990, AlHammadi 1992. Moreover, Kuwait was not part of any regional or any international conflicts including both World Wars, and didn't require an armed revolution for independence. The declaration of independence was smoothly approved by Great Britain in 1961. However, Kuwait was attacked several times by neighboring Iraq and the tribes from the interior of Arabia, but these attacks were small enough to be repulsed.

The invasion and occupation of Kuwait by Iraq in 1990 and 1991 had both historical and economic causes. Iraqi governments since the Othmani Empire have held the belief Kuwait is part of Iraq and that Great Britain had taken it from them. This was also true when Iraq was a Kingdom in 1920's and an unsuccessful trial to invade Kuwait was held. These trials were repeated through the different republic governments in Iraq after the decline of the Kingdom, Al-Hammadi (1992). They were also unsuccessful due to the Protection Treaty (1899) between Kuwait and Great Britain that limited these trials. The last trial was in 1971 when Iraq occupied a border police station but withdrew immediately after Great Britain promised an immediate military response. These historical Iraqi beliefs are a central goal regardless of what government comes to power. The second main reason for the invasion was the economic problems Iraq was going through after the long war with Iran was putting pressure on Kuwait; Iraq was blackmailing Kuwait and asking for more support, and blaming Kuwait and Saudi Arabia for the decline in the oil prices at that time. This was happening even though Kuwait and all the Gulf States including Saudi Arabia had supported the Iraqi government during that war.

On August 2, 1990, the government of Iraq decided to invade and occupy Kuwait with 500,000 million soldiers. The extent of the invasion and occupation of Kuwait was not expected by the population; Sadam had not threatened to eradicate the state and make it the 19th province of Iraq as yet. The people of Kuwait were not prepared for the catastrophe that created psychological, social, and financial imbalance. The occupation continued till the liberation by the allied forces headed by the United States of America in February 26, 1991.

2. Traumatic Events As a result of the Invasion and Occupation

2. A. Characteristics of the trauma

As a result of the surprise invasion, 6 hours after troops crossed the border the whole of Kuwait was occupied while the people slept. At 8 a.m., August 2, 1990, the troops were spread out at checkpoints on the main streets of Kuwait. This was the biggest shock that's ever happened to the Kuwaiti people.

This trauma has specific characteristics that made it severely distressing to the population. These characteristics can be summarized as follows:

1. Iraq as a neighboring country shares the same Arab background. Most of the tribes in Iraq have relatives that are Kuwaitis and they also share same religions: Muslims: Suny, Sheeaa, and Christian.

2. The Kuwaiti government and people supported the Iraqi people and government during the Iraq and Iran war. Billions of dollars from the Generations Funds were spent on that conflict.

3. The demands by Sadam that there will be no State of Kuwait, and that it be called province no.19, and all Kuwaiti people be called "New Iraqis", and that they should be re-issued all their documents, ID's, and birth certificates.

4. People inside Kuwait had no contact with their relatives outside the country after the third day of occupation.

5. The people of Kuwait had no experience dealing with crises: not the government or the general population. Even the ambulances were working with minimal capacity and efficiency, as they were not able to cope with the mass injuries and traumas.

6. Loss of security and safety for self, home, and children that was dramatic and within hours created a feeling of instability among many citizens. Where to go was the question in the minds of the people who stayed or those who left Kuwait.

7. The invasion and occupation was so rapid that it didn't leave much time for people to make proper decisions concerning their fates and those of their families.

2. B. Statistics of the Injuries

The following are the traumatic consequences of this war:

1. Executions:

There were over 600 executions during the invasion and occupation period Al-Hammadi 1994. Of almost all of the 600 executed Kuwaiti citizens, the executions were (by force of the Iraqi intelligence) witnessed by family members like spouses, children, parents, and neighbors, plus whoever else was available. The events were highly traumatic for those who witnessed them. Bodies were left for about 24 hours at the site. Another 600 missing individuals turned out to be executions at the hands of the regimen, discovered in the period when the Iraqi regime was overthrown in 2004.

2. POWs

There were about 15,500 POWs that were released since the invasion and occupation of Kuwait. These POWs were released during different periods.

There were many causes for detention for these POWs (Al-Hammadi, 1994). We can summarize them as follows:

A. Resistance—armed or civil.
B. Membership in the police or army
C. Disobeying the orders of the army
D. Demonstration
E. Being a Politician
F. Taking documentary photographs

The torture tools included (these tools were retrieved after the liberation and kept in the museum):

A. Electric tools
B. Burning devices
C. Chemicals
D. Cutting tools

Torture methods included (Al-Hammadi, 1994):

A. Sexual, this was applied to both male and female POWs
B. Applying electric current to the genitalia
C. Burns
D. Cutting and nail removal
E. Beating
F. Hanging for long periods of time from the hands or the legs
G. Witnessing others being tortured, bringing the family members to watch, and threatening torture, execution, or deprivation.

3. Mine injuries:

Mines were planted inside and all around Kuwait. Nearly 1,400 individuals suffered injuries from them. These injuries caused amputations to upper and/or lower limbs or part of limbs.

4. Physical Injuries:

It is estimated that there were 1,600 injured during the invasion and occupation of Kuwait (Al-Hammadi, 1994). There were many causes for physical injuries. Armed resistance, torture, and mine injuries were among the most common causes.

5. Other injuries:

A. Oil fires: Started in February 1991 and put out in November, the smoke from these fires could have an impact on the general health of the population who has inhaled large quantities of the aromatic hydrocarbons. No study so far has correlated the levels of these substances and physical or psychological problems.

B. There was a suspicion at that time that the tanks and cargo cars of the Iraqi army left in the civilian areas were contaminated with radioactive material. Their impact was not investigated.

C. The soldiers were given vaccinations for the "biological" and/or chemical threats. The impacts of these vaccinations on their physical and psychological health have not been studied.

3. Kuwait Liberation

Kuwait was liberated on February 26,1991. This came after extensive efforts from inside and outside Kuwait.

A. Inside Kuwait:

This was the most traumatic for the population and cost most of the fatalities, injuries, arrests, tortures, and almost all of the combat injuries for the Kuwaiti population. Immediately after the invasion and occupation, Kuwaitis created resistance cells that worked in two main lines: civil and armed resistance.

Armed fighting occurred almost daily all over Kuwait. Moreover there were many explosions organized by the resistance against the Iraqi soldiers.

B. Outside Kuwait

The government outside Kuwait gathered the Allies for the liberation which used a multinational military force starting January 17, 1991 to February 26,1991.

4. Review of Literature

4. A. Introduction:

The Allied coalition consisted of 34 countries including Afghanistan, Argentina, Australia, Bahrain, Bangladesh, Canada, Czechoslovakia, Denmark, Egypt, France, Germany, Greece, Hungary, Honduras, Italy, Kuwait, Morocco, The Netherlands, Niger, Norway, Oman, Pakistan, Poland, Portugal, Qatar, Saudi Arabia, Senegal, South Korea, Spain, Syria, Turkey, The United Arab Emirates, the United Kingdom and the United States (CNN.com website).

The U.S. had more than 500,000 troops in the Gulf War, while the rest of the coalition forces equaled roughly 160,000 (or 24 %), of all forces (CNN.com website).

There were multiple health concerns other than combat injuries. The following are the health concerns due to the war:

1. Combat:

U.S. casualties were: 148 battle deaths, 145 non-battle deaths. There were: Army: 98 battle; 105 non-battle, Navy: 6 battle; 8 non-battle, Marines: 24 battle; 26 non-battle, Air Force: 20 battle; 6 non-battle, Women killed: 15, U.S. wounded in action: 467, British casualties: 24, nine by U.S. fire, British wounded in action: 10, French casualties: 2, French wounded in action: 25 (estimated), Allied Arab casualties: 39, Allied combat air sorties flown: More than 116,000, Coalition aircraft losses: 75 (63 U.S., 12 Allied), Fixed wing: 37 combat, 15 non-combat (U.S. losses -- 28 combat, 12 non-combat; no U.S. losses in air-to-air engagements), Helicopters: 5 combat, 18 non-combat (all U.S.), (CNN.com website).

2. Gulf Oil Fires:

Before withdrawing from Kuwait, Iraqi troops set fire to over 700 oil wells causing a huge environmental pollution crisis and concerns about the smoke spreading from these fires (AlHammadi 1992).

Researchers from the Centers for Disease Control and Prevention (CDC) and several other federal agencies conducted surveys of workers in Kuwait City in May 1991 and of firefighters in the oil fields in October of the same year. Blood samples were tested for 31 volatile organic compounds (VOCs) and compared with samples from a control group living in the United States. The United State's samples were collected as part of the Third National Health and Nutrition Examination Survey (NHANES III), a national survey of American health. The median concentration of VOCs among the firefighters was elevated. However, among the non-firefighting personnel, VOC concentrations were equal to or lower than the levels found among those in the United States, Centers for Disease Control and Prevention, U.S.A.

3. Endemic infectious diseases and biological warfare during the Gulf War:

Hyams et al (2001) reported that, "Infectious diseases were one of the first health threats confronted by Coalition troops deployed to the Arabian Desert in August 1990. On the basis of experiences in World War II, the major endemic infectious disease risks were thought to be sand fly fever, cutaneous leishmaniasis, diarrhea disease, and malaria. Although there was active surveillance, no case of sand fly fever and few other endemic infectious diseases were identified among over 500,000 U.S., British, and Canadian ground troops. In addition, there was no diagnosis of biological warfare (BW) exposure, and BW agents were not detected in clinical, environmental, or veterinary samples. The most common infectious disease problems were those associated with crowding (acute upper respiratory infections) and reduced levels of sanitation (travelers-type diarrhea). Only one endemic infectious disease has been confirmed as causing chronic health problems: visceral Leishmania tropica infection (viscerotropic leishmaniasis). However, this protozoan infection was diagnosed in only 12 U.S. veterans, and no new cases have been identified during the last 8 years. Infectious diseases were not a serious problem for Gulf War troops because of extensive preventive medicine efforts and favorable weather and geographic factors. Moreover, it is unlikely that an endemic infectious disease or a BW agent could cause chronic health problems and remain undetected over a 10-year period Hyams et al 2001**"**.

4. Chemical and Nuclear threats:

Alexander (2000) included both chemical and nuclear threats as part of ecoterrorism combined with other nontraditional threats that may increase with military buildups in war and peacetime. The availability of devastating biological, chemical, and radioactive agents also increases, and adversaries or terrorist groups are more inclined to use them. Before the Gulf War, an act of ecoterrorism performed by the Iraqi regime was documented in north of Iraq against Kurds where the regime used chemical weapons. The whole world observed the consequences of their use. Because these consequences were so fearful, vaccination for the soldiers preparing to face such threats was postulated. It was proposed these preparations triggered multiple medical and psychological consequences after the war.

Soldiers participated in FGW in 1990-1991 reported multiple health problems after the war ended and during follow up examinations, DeFraites (1992). Relationship of physical symptoms to PTSD has important clinical implications for veterans with persistent or undiagnosed physical symptoms since serving in the FGW Engel et al (2000). The following is a review of the literature of the psychological and physical complications of the First Gulf War (FGW).

The Iowa Persian Gulf Study Group (1997) studied a total of (4886) subjects who were randomly selected from (1 of 4) study domains (regular military, National Guard/Reserve, non-Gulf War regular military, and non-Gulf War National Guard/Reserve), stratifying for age, sex, race, rank, and branch of military service, to assess the prevalence of self-reported symptoms and illnesses. Of the total sample (76%) completed the telephone interview. Compared with non-gulf war military personnel, gulf war military personnel reported a significantly higher prevalence of symptoms of depression (17.0% vs. 10.9%), (P<. 001), posttraumatic stress disorder (PTSD) (1.9% vs. 0.8%, P=. 007), chronic fatigue (1.3% vs. 0.3%, P<. 001), cognitive dysfunction (18.7% vs. 7.6%, P<. 001), bronchitis (3.7% vs. 2.7%, P<. 001), asthma (7.2% vs. 4.1%, P=. 004), fibromyalgia (19.2% vs. 9.6%, P<. 001), alcohol abuse (17.4% vs. 12.6%, P=. 02), anxiety (4.0% vs. 1.8%, P<.001), and sexual discomfort (respondent, 1.5% vs. 1.1%, P=.009; respondent's female partner, 5.1% vs. 2.4%, P<.001). They concluded there were larger differences between Gulf War and non-Gulf War military personnel in the postwar psychological and physical symptom arenas. Friedman et al (1994) put forth the following conclusions studying the consequences of FGW on veterans:

a. Military personnel exposed to war-zone trauma are at risk for developing PTSD. Those at greatest risk were exposed to the highest levels of war-zone stress, those wounded in action, those captured and kept as prisoners of war, and those who manifest acute war-zone reactions.

b. In addition to problems directly attributable to PTSD, individuals with this disorder frequently suffer from other co-morbid psychiatric disorders such as depression, other anxiety disorders, and alcohol or substance abuse/dependence. The resulting constellation of psychiatric symptoms frequently impairs marital, vocational, and social function.

c. The likelihood of developing chronic PTSD depends on pre-military and post-military factors in addition to exposure to war zone trauma. Pre-military factors include negative environmental factors in childhood, economic deprivation, family psychiatric history, age of entry into the military, pre-military educational attainment, and general personality characteristics. Post-military factors include social support and the individual veteran's coping skills.

d. American military personnel from three populations risk unique problems that may amplify the psychological impact of war-zone stress. They are women whose war-zone experiences may be complicated by sexual assault and harassment; nonwhite ethnic minority individuals whose pre-military, post-military, and military experience is affected by racism; and those with war-related physical disabilities whose PTSD and medical problems often exacerbate each other.

e. The longitudinal course of PTSD varies quite a bit. Some trauma survivors may achieve complete recovery, while others may develop a persistent mental disorder that severely and chronically incapacitates them. Other patterns include delayed, chronic, and intermittent PTSD.

f. Theoretically, primary preventive measures might include prevention of war and/or screening out vulnerable military recruits. In practice, primary preventive measures have included psychoeducational and inoculation approaches. Secondary prevention has been attempted through Critical Incident Stress Debriefing administered according to the principles of proximity, immediacy, expectancy, and simplicity. Tertiary prevention has included psychotherapy, pharmacotherapy, dual diagnosis approaches, peer counseling, and inpatient treatment. Few of these treatments have been rigorously evaluated.

g. There are both theoretical reasons and empirical findings suggesting military veterans with PTSD are at greater risk for more physical health problems, poorer health status, and more medical service usage. Much more research is needed on this matter.

h. Despite the potential adverse impact of war-zone exposure on mental and physical health, there is also evidence trauma occasionally has salutary effects on personality and overall function.

4. B. Psychiatric consequences of First Gulf War

Lee et al (2002) studied (3000) British veterans who had sought advice from a special medical assessment program established because of the alleged Gulf War Syndrome. These were classified as: completely well, well with symptoms and controlled, or unwell (physically or mentally). A psychiatrist confirmed the diagnosis of mental illness. The study found the following: Post-traumatic stress disorder (12%): Without co-morbidity (8%), with co-morbidity (5%): Depression (3%), Alcohol abuse (2%), and Substance abuse (1%). Depression (6%), Alcohol abuse (2%), Substance abuse (1%), Adjustment disorders (2%), Anxiety disorders (1%), Reaction to severe stress (0%), other psychiatric disorders (1%), No formal psychiatric diagnosis (8%).

Stretch et al (1996) assessed the prevalence of risk for development of post-traumatic stress disorder (PTSD) symptoms among active duty and reserve veterans from Pennsylvania and Hawaii who had either deployed (N = 1,524) or did not (N = 2,727) to the FGW. They have used the Impact of Event Scale and the Brief Symptom Inventory. Results of this study indicated that the likelihood of PTSD symptoms is approximately (8.0%) in the active duty veterans and (9.3%) in the reserve veterans who deployed.

Clinical evaluation of more than 80 000 veterans and initial epidemiologic surveys have identified a broad range of health problems, including symptoms of post-traumatic stress disorder in (5% to 15%) of some veteran populations; Labbate (1992) Perconte et al (1993), Sutker et al (1993), Southwick et al (1993).

Veterans of the FGW present various symptoms and maladies Jamil et al (2006). By studying Iraqi FGW veteran refugees living in the US, they found a relationship between PTSD scores

and health outcome measures of chronic fatigue, fibromyalgia, functional status, quality of life, and health care utilization in terms of frequency and level of intensity.

In (1991) the Department of Veterans Affairs USA published the results of the assessment of the first 328 FGW veterans who were seen by the Veterans Administration Readjustment Counseling Service. They found that (55) had war-related acute stress reaction, (10) had other psychological problems, (5%) were found to have PTSD, six months after homecoming. Individuals who had difficulty discussing their experiences with more than one person also showed significantly higher PTSD scores.

To assess the prevalence of and risk factors for current anxiety disorders in FGW veterans, Black et al (2004-a) administered a structured telephone interview to a population-based sample of 4886 military personnel from Iowa at enlistment: Gulf War National Guard/ Reserve, non-Gulf War regular military, and non-Gulf War National Guard/Reserve. They found FGW veterans reported a markedly higher prevalence of current anxiety disorders than non-deployed military personnel (5.9% vs. 2.8%; odds ratio = 2.1; 95% confidence interval = 1.3-3.1), and their anxiety disorders were associated with co-occurring psychiatric disorders. PTSD, panic disorder, and generalized anxiety disorder were present at nearly twice the expected rates. FGW combat was independently associated with current posttraumatic stress disorder, panic disorder, and generalized anxiety disorder. They concluded current anxiety disorders are relatively frequent in a military population and are more common among First Gulf War veterans than non-deployed military personnel.

4. C. Physical Consequences of FGW

Traumatic combat experience has been associated with the development of posttraumatic stress disorder, but there have been few studies about the association of military combat experience and the development of somatoform disorders Labbate et al (1998). They evaluated (131) referred FGW veterans for medical and psychiatric syndromes suspected to be related to the war. Patients completed questionnaires regarding their traumatic experiences and were interviewed using the Structured Clinical Interview for DSM III-R. They found that (69%) had Axis-I conditions: Major depression, undifferentiated somatoform, and posttraumatic stress disorders were the most common diagnoses. They proposed that psychiatric syndromes could explain some medical

complaints. These results suggest some psychological and nonspecific somatic symptoms persisting since the Gulf War may be related to psychological trauma.

Studies in the literature have focused on the importance of exposure during the Gulf War to environmental hazards other than the injury itself. The Gulf War veterans were exposed to: smoke from burned excrement, burning oil wells, toxic paints and pesticides, depleted uranium, infectious agents, chemo prophylactic agents, immunizations, and perhaps even chemical or biological warfare agents NIH (1994).

4. C. 1. Studies supporting the neurotoxin and environmental exposure as etiological factors:

Baker et al. (1997) found that physical symptoms were strongly related to a diagnosis of PTSD among a group of (188) FGW veterans. The (13%) of veterans with PTSD were (4.8 to 16) times more likely to report different physical symptoms, but these physical symptoms were not attributed to medical illness or other possible environmental factors.

Engel et al (2000) assessed (21,244) FGW veterans seeking care for war-related health concerns to assess the relationship of PTSD to physical symptoms independent of environmental exposure reports and medical illness. They found that PTSD veterans had an average of (6.7 SD = 3.9) physical symptoms, those with a non-PTSD had (5.3 SD=3.5) physical symptoms, those with medical illness had (4.3 SD=3.4) physical symptoms, and the control "healthy" group had (1.2 SD=2.2) physical symptoms. The PTSD veterans' physical symptoms were independent of demographic characteristics, veteran-reported environmental exposures, and co-morbid medical conditions.

Increased health symptoms were reported by US veterans after the FGW Proctor. In their study Proctor et al (1998) investigated the relationships between several FGW environmental exposures and health symptom reporting, and the role of traumatic psychological stress on the exposure-health symptom relationships. They used stratified, random samples of two cohorts of FGW veterans. One group came from the New England area (n = 220) and the other from the New Orleans area (n = 71), and both were selected from larger cohorts being followed longitudinally since arrival home from the Gulf. A control group of FGW veterans deployed to Germany (n = 50) served as a comparison group. They found the prevalence of reported

symptoms was greater in both FGW deployed cohorts when compared to the Germany cohort. Analyses of the body-system symptom scores (BSS), weighted to account for sampling design, and adjusted by age, sex, and education, indicated FGW deployed veterans were more likely to report neurological, pulmonary, gastrointestinal, cardiac, dermatological, musculoskeletal, psychological and neuropsychological system symptoms than the Germany veterans. Using a priori hypotheses about the effects of exposure to specific toxicants, the relationships between self-reported exposures and body-system symptom groupings were examined through multiple regression analyses, controlling for war-zone exposure and PTSD. Self-reported exposures to pesticides, debris from Scuds, chemical and biological warfare (CBW) agents, and smoke from tent heaters each were significantly related to increased reporting of specific predicted BSS groupings. They concluded the veterans deployed have higher self-reported prevalence of health symptoms compared to FGW veterans who went only as far as Germany. Several Gulf-service environmental exposures are associated with increased health symptom reporting involving predicted body-systems, after adjusting for war-zone stressor exposures and PTSD.

Another study by Simmons et al (2004) confirmed FGW veterans reported higher rates of general ill health. They examined self-reported adult ill health in a large sample of male UK FGW veterans and a demographically similar non-deployed comparison group, exploring self-reported ill health among veterans who believed they suffered from Gulf War syndrome. This was part of a retrospective cohort study of reproduction and child health in which a validated postal questionnaire was sent to all UK FGW veterans and a comparison cohort of Armed Service personnel not deployed. The cohort for analysis comprises (42,818) males who responded to the questionnaire. They found that FGW veterans were significantly more likely to have reported at least one new medical symptom or disease since 1990 than non-FGW veterans (61% versus 37%, OR 2.7, 95% CI 2.5-2.8). They were also more likely to report a higher number of symptoms. The strongest associations were for mood swings (OR 20.9, 95%CI 16.2-27.0), memory loss/lack of concentration (OR 19.6, 95% CI 15.5-24.8), night sweats (OR 9.9, 95% CI 6.5-15.2), general fatigue (OR 9.6, 95% CI 8.3-11.1) and sexual dysfunction (OR 4.6, 95%CI 3.2-6.6). 6% of FGW veterans believed they had Gulf War Syndrome (GWS), and this was associated with the highest symptom reporting.

White et al (2001) found that there are subtle differences in CNS function among FGW deployed veterans who reported chemical warfare agent exposure. General intellectual abilities tested included: Attention and executive function, Motor/psychomotor function, visuospatial abilities,

memory, mood and motivation. The study concluded central nervous system dysfunction and lower performance on neuropsychological tests were directly related to specific neurotoxicant exposures.

4. C. 2. Studies not supporting the neurotoxin and environmental exposure as etiological factors:

Ishoy et al (2004) tested the hypotheses that FGW veterans would perform less well than controls using a computerized neuromotor test battery; and that FGW veteran's psychological profiles are different from that of controls. They used a cross-sectional study of (686) subjects who had been deployed in the FGW within the period August 2, (1990) until December 31, (1997) (six years after the war ended); the control group comprised (231) subjects matched by age, gender, and profession. All participants underwent clinical examinations, along with a neuromotor test battery and a psychological health status questionnaire, the SCL-90-R rating scale. They found no differences between FGW veterans and controls with respect to lifestyle and cohabitation characteristics. Differences between the two groups with respect to neuromotor function were negligible. Within the GW veteran group, stratified according to clustering of neuropsychological symptoms, and stratified according to SCL-90-R score, no trends were found suggesting reduced motor function with increasing symptoms. Of nine dimensions constructed on the basis of the SCL-90-R items, (6) were significantly associated with being a FGW veteran. Statistically, the strongest associations were found for ratings of the obsessive-compulsive and depression dimensions. No associations were found with respect to phobic anxiety, paranoid ideation, and psychoticism. They concluded the increased psychological distress found among Danish GW veterans was a result of a mentally distressing environment rather then neurotoxic exposure.

In a national cross-sectional cohort study Eisen (2005) of deployed and non-deployed FGW veterans who were evaluated by direct medical and tele-dermatologic examinations. This study was performed 10 years after the 1991 Gulf War. Deployed (n = 1061) and non-deployed (n = 1128) veterans were examined at 1 of 16 Veterans Affairs medical centers. Only 4 conditions were more prevalent among deployed than non-deployed veterans: fibromyalgia (deployed, 2.0%; non-deployed, 1.2%; odds ratio, 2.32 [95% CI, 1.02 to 5.27]); the chronic fatigue syndrome (deployed, 1.6%; non-deployed 0.1%; odds ratio, 40.6 [CI, 10.2 to 161]); dermatologic conditions (deployed, 34.6%; non-deployed, 26.8%; odds ratio, 1.38 [CI, 1.06 to 1.80]), and

dyspepsia (deployed, 9.1%; non-deployed, 6.0%; odds ratio, 1.87 [CI, 1.16 to 2.99]). The mean physical component summary score of the SF-36 for deployed and non-deployed veterans was 49.3 and 50.8, respectively.

A cross-sectional study of 1456 Australian Gulf War veterans was carried out with a comparison group who were in operational units at the time of the Gulf War but were not deployed to that conflict (n = 1588). A postal questionnaire was administered and the likelihood of the diagnosis of self-reported medical conditions was assessed and rated by a medical practitioner Kelsal et al (2004). They found that 10 years after the 1991 Gulf War, Australian veterans self-reported all symptoms and some medical conditions more commonly than the comparison group. Main messages given by this study were:

- Australian Gulf War veterans reported all symptoms more commonly than expected, and more of the Gulf War veterans reported severe symptoms.
- Australian Gulf War veterans report psychological (particularly post-traumatic stress disorder), skin, eye, and sinus conditions more commonly than expected.
- The likelihood of the diagnosis of self-reported medical conditions is high in both study groups, and increased reporting of medical conditions by Gulf War veterans does not appear to be explained by over-reporting.
- Increased symptom reporting in Gulf War veterans is associated with several medical, environmental, and chemical exposures and stressful military service experiences reported.

Unwin et al (1999) gave a possible explanation for the development of physical symptoms among FGW veterans, proposing it could be due to an unfamiliar hostile environment. A specific mechanism may link vaccination against biological warfare agents and ill health. They investigated UK servicemen through a cross-sectional postal survey on a random sample of FGW veterans (FGW cohort, n=4248) and, stratified for age and rank, servicemen deployed to the Bosnia conflict (Bosnia cohort, n=4250) as well as those serving during the FGW but not deployed there (Era cohort, n=4246). There were (8195, 65.1%) valid responses. The FGW cohort reported symptoms and disorders significantly more frequent than those in the Bosnia and Era cohorts. Those two were similar. Perception of physical health and ability were significantly worse in the FGW cohort than in the others, even after adjustment for confounders. FGW veterans were more likely than the Bosnia cohort to have substantial fatigue (odds ratio 2.2 [95%

CI 1.9-2.6]), symptoms of post-traumatic stress (2.6 [1.9-3.4]), and psychological distress (1.6 [1.4-1.8]), and were nearly twice as likely to reach the CDC case definition (2.5 [2.2-2.8]). In the FGW, Bosnia, and Era cohorts, respectively, (61.9%, 36.8%, and 36.4%) met the CDC criteria, which fell to (25.3%, 11.8%, and 12.2%) for severe symptoms. The FGW cohort reported potentially harmful exposures the most. All exposures showed associations with all of the outcome measures in the three cohorts.

4. D. Depression

Depression is a common mental disorder associated with poor health outcomes Black et al (2004-b). They examined the prevalence of depression, mental health co-morbidity, illness variables, and quality of life, using a sample of military veterans serving during the FGW. There were (602) military personnel in the sample, either deployed or non-deployed veterans. One hundred ninety-two (32%) of the 602 surveyed veterans met criteria for a current or lifetime depressive disorder (major depression, dysthymia, or a depressive disorder not otherwise specified). Depressed non-deployed veterans were more likely to be female and to have served in the Air Force than depressed deployed veterans. There were few significant differences between the depressed deployed veterans and the depressed non-deployed veterans. Depressed deployed veterans had significantly higher lifetime rates of co-morbid cognitive dysfunction (55% vs. 35%), and anxiety disorders (59% vs. 33%) that were mainly accounted for by specific phobias (12% vs. 2%) and posttraumatic stress disorder (33% vs. 10%) than did depressed non-deployed veterans. Lifetime substance use disorders were significantly more frequent in deployed veterans than non-deployed veterans (70% vs. 52%), particularly alcohol disorders (68% vs. 52%). There were no differences in rates of personality characteristics, family psychiatric history, stressors, hypochondriasis, and the level of functioning between the two study groups showed no significant differences. Depressive illness is common in military samples and the general population. The prevalence, pattern of co-morbidity, and illness features, were similar in deployed veterans and non-deployed veterans, suggesting that the depression suffered by both groups is qualitatively comparable. The main difference between studied groups was depressed deployed veterans had higher rates than depressed non-deployed veterans of co-morbid anxiety disorders; this was hypothesized to be part of the stress-related syndromes seen in those who experience combat.

4. E. Conclusion:

In Kuwait the mass destruction of the infrastructure and the relatively huge number of captured, tortured, injured, and executed persons, both military and civilian, had led to an interest in studying the psychological complications of the FGW. In Kuwait, the last oil fire was put off on November 1991, after 9 months of hard work to extinguish over 700 oil wells. The fear of physical and psychological ill health from the inhaled toxins of these fires was an additional impetus to conduct such studies. The Kuwaiti military divided into two groups: one that joined the allies outside the country, and the second who formed the resistance with the civilians inside Kuwait. The vaccinations the outside military personnel took were also a concern to health officials in Kuwait. The fear of depleted uranium from damaged and destroyed military vehicles and the possible contamination of soldiers and civilians was also a concern for health officials. The allies who did intensive investigations to find answers shared the fear of possible consequences from all these hazards. They wanted to know if there were physical and/or psychological consequences for both the military and non-military personnel. In this study, we looked at the psychological consequences of the FGW on a sample of the injured Kuwaiti population who participated in the war.

II. PTSD Study in Kuwait

The first epidemiological study conducted in Kuwait on the effects of FGW was in 1993 (Al-Hammadi et al 1993). This study reported the prevalence of psychopathology after the liberation (2 ½ years after the trauma), due to the traumatic events suffered during that period. In this study, the effect of different traumatic events was studied: torture, rape, and physical injury, going into hiding, and different fears. Using the Impact of Event Scale, 27.1% of the population at that time scored above the cut off point for posttraumatic stress disorder (PTSD), and 48.5% scored above the cut off point for depression using Hopkins checklist -25. The rates of PTSD were higher in specific traumatic events, e.g. family members of the martyrs (executed) 42.5%, POWs 32.7%, and injured 33.7%.

The previous study was repeated on the same sample (cohort), and comparing the results of the two periods (5 years apart) it was found that:

1. PTSD: (Table 1)
Cases who recovered from PTSD by 1998 = 143 (10.2% of the total 1401 Cases)
Cases who developed PTSD by 1998 = 261 (19.6% of the total 1401 Cases)
Chronic cases 8.7%
Pearson Chi-Square = 57.53, $p < .001$

2. Depression: (Table 2)
Cases who recovered from DEP by 1998 = 349 (30.8% of the total 1134 Cases)
Cases who developed DEP by 1998 = 69 (6.1% of the total 1134 Cases)
Chronic cases 19.0%
Pearson Chi-Square = 102.21, $p < .001$

3. Anxiety: (Table 3)
Cases who recovered from ANX by 1998 = 371 (32.4% of the total 1146 Cases)
Cases who developed ANX by 1998 = 62 (5.4% of the total 1146 Cases)
Chronic cases 14.7%
Pearson Chi-Square = 78.73, $p < .001$

Table. 1. Comparison between prevalence PTSD 1993 and PTSD 1998

	PTSD 1998 = NO	PTSD 1998 = YES	Total Valid Cases
	N Row % Column % Total %	N Row % Column % Total %	Row Total (N) Column %
PTSD 1993 = NO	875 77% 86% 62.5%	261 23% 68.1% 18.6%	1136 81.1%
PTSD 1993 = YES	143 54% 14% 10.2%	122 46% 31.9% 8.7%	265 18.9%
Column Total **Row %**	1018 72.7%	383 27.3%	1401 100%

Cases who recovered from PTSD by 1998 = 143 (10.2% of the total 1401 Cases)
Cases who developed PTSD by 1998 = 261 (19.6% of the total 1401 Cases)
Chronic cases 8.7%
Pearson Chi-Square = 57.53, $p < .001$

Table. 2. Comparison between prevalence Depression 1993 and Depression 1998

	DEP 1998 = NO	**DEP 1998 = YES**	**Total Valid Cases**
	N **Row %** **Column %** **Total %**	**N** **Row %** **Column %** **Total %**	**Row Total (N)** **Column %**
DEP 1993 = NO	501 87.9% 58.9% 44.2%	69 12.1% 24.3% 6.1%	570 50.3%
DEP 1993 = YES	349 61.9% 41.1% 30.8%	215 38.1% 75.7% 19.0%	564 49.7%
Column Total **Row %**	850 75%	284 25.0%	1134 100%

Cases who recovered from DEP by 1998 = 349 (30.8% of the total 1134 Cases)
Cases who developed DEP by 1998 = 69 (6.1% of the total 1134 Cases)
Chronic cases 19.0%
Pearson Chi-Square = 102.21, $p < .001$

Table. 3. Comparison between Anxiety 1993 and Anxiety 1998

	ANX 1998 = NO	**ANX 1998 = YES**	**Total Valid Cases**
	N **Row %** **Column %** **Total %**	**N** **Row %** **Column %** **Total %**	**Row Total (N)** **Column %**
ANX 1993 = NO	544 89.8% 59.5% 47.5%	62 10.2% 26.8% 5.4%	606 52.9%
ANX 1993 = YES	371 68.7% 40.5% 32.4%	169 31.3% 73.2% 14.7%	540 47.1%
Column Total **Row %**	915 79.8%	231 20.2%	1146 100%

Cases who recovered from ANX by 1998 = 371 (32.4% of the total 1146 Cases)
Cases who developed ANX by 1998 = 62 (5.4% of the total 1146 Cases)
Chronic cases 14.7%
Pearson Chi-Square = 78.73, $p < .001$

Chapter III. Methods

1. Aims of the study:

The study was designed to investigate the prevalence of Post-traumatic Stress Disorder (PTSD) and other psychological morbidities and the hormonal changes: (cortisol and thyroid) that may accompany such disorder among surivors Kuwaiti FGW injured personnel. It is also aimed to study whether these victims have a higher that expected rate of PTSD and other psychological morbidity, and whether these post trauma adverse effects are associated with exposures and experiences that these victims experienced during FGW. The main objectives of the study were:

1. To investigate the contribution of traumatic injury to the neurobiology of PTSD:

   A. To investigate the level of morning cortisol in association with PTSD.

   B. To investigate the levels of free thyroxine (fT4), free triiodothyronine (fT3), and Thyroid stimulating hormone (TSH) in association with PTSD.

2. The prevalence rate of PTSD, depression, anxiety and other psychological morbidity among physically injured victims.

3. The prevalence of symptoms, cluster of symptoms and medical conditions, and psychosomatic conditions that is related to the current mental health state and previous exposure to traumatic events during or after FGW.

2. A. Hypotheses:

The study was designed to answer the following questions related to PTSD:

1. What is the prevalence of PTSD and other psychological comorbidities between FGW injured survivors?

2. What is the role of cortisol hormone level in patients with chronic PTSD to maintain chronicity of this disorder?

3. What is the thyroid functions fT4, fT3, and TSH in war injured patients with chronic PTSD?

The following are the study hypotheses:

2. B. 1. PTSD

Prevalence of PTSD and other psychological comorbidities between FGW injured survivors:

The following are the hypotheses:

A. War injured survivors with Chronic PTSD have cluster of symptoms severity similar to that found patients with delayed onset PTSD after 13 years of the trauma.
B. The prevalence of chronic PTSD is maintained in its rate during the course time for the population.
C. There are psychosocial factors that may maintain the chronicity of PTSD
D. The rate of recovery is low
E. The presence of axis-II disorders influences chronicity of PTSD
F. Co-morbid disorders are high with chronic PTSD

2. B. 2. Cortisol levels in patients with chronic PTSD:

The following hypotheses for the association between chronic PTSD and Cortisol:

A. Patients with chronic PTSD have low cortisol levels, which are compared to those with delayed onset PTSD or lifetime PTSD.

B. Patients who completely recovered from PTSD may have normalizes there cortisol levels whereas patients with partial recovery, cortisol levels changes may persist.

C. Co- morbid psychiatric disorders with PTSD disorders may have an impact on cortisol levels.

D. Degree of disability, age, and duration and severity of PTSD symptoms may not have an effect on cortisol level.

2. B. 3. Thyroid functions: fT4, fT3, TSH in patients with chronic PTSD:

Patients with chronic type of PTSD have different thyroid activity compared to those with acute PTSD or lifetime PTSD. The recovery of hyperarousal PTSD symptoms had no effect on thyroid functions. Type of trauma, degree of disability, age, and duration of PTSD symptoms if it remains chronic will not affect thyroid functions. Thyroid profiles in PTSD may be activated or suppressed based on the adaptive responses determined by the environmental constrains. The hypotheses are:

Thyroid functions: free thyroxin (fT4), free triiodothyronin (fT3), and thyroid stimulating hormone (TSH) in patients with PTSD: The hypotheses are:

A- Patients with PTSD have different HPT axis activity throughout the course of this disorder: delayed and chronic PTSD

B- Patients with chronic type of PTSD have stable thyroid activity compared to those with acute PTSD

C- Patients who recovered from PTSD have normal thyroid functions regardless of the hyperarousal, avoidance or intrusive PTSD symptoms remaining after the recovery phase.

D- Co- morbid psychiatric disorders associated with PTSD had minor effect on HPT axis in patients with chronic PTSD.

E- Degree of disability, age, and duration of PTSD symptoms could have an effect on the HPT axis.

The following parameters will be tested: fT3, fT4 and TSH. The following groups of participants in association with PTSD: Delayed onset PTSD, chronic PTSD, recovered (lifetime) PTSD, and participants without PTSD diagnosis.

3. Design and Stages

This is a prospective study of a cohort sample of injured Kuwaiti FGW survivors designed to investigate the prevalence of psychiatric morbidity due to exposures to traumatic events. The study included two main phases:

3. A. First Phase:

This assessment phase was conducted in 1998 and involved a thorough interview by the principal investigator: Abdullah Al-Hammadi, which included the extent and exact causes of the injury, its consequences, and extent of disability. The injured were also assessed for the presence of psychological disorders by face-to-face interview and self-rating questionnaires. The (6 to 65) years old family members were also assessed. All of the registered Kuwaiti war-injured victims at the Social Development Office (caring for former war injured survivors) were approached. Out of (234) individuals (212, 90.5%) war-injured subjects agreed to participate in the study. They were injured either due to combat, due to torture or when they were POWs. Some were members of the Kuwaiti armed forces at the time of the invasion, others were members of the resistance, others were civilians uninvolved in the resistance, but caught up in events. Family members who were assessed in the first phase of the study included 467 adults and 203 children.

3. B. Second Phase:

This reassessment phase done in 2003 and this phase of the study will be discussed in this report. The same sample of FGW-injured survivors tested in the first phase were approached and reassessed in the second phase. The reassessment involved an interview with psychiatric examination, blood tests, and applying mental health questionnaires that were used in the first phase. The 212 war-injured participants were approached for reassessment. The family members were not included in this part of the study.

4. Sample

The FGW injured victims were physically injured during the invasion and occupation period of Kuwait (2nd August 1990-26th February 1991) due to combat, resistance, and torture; or after the liberation due to mine injuries. They were civilians or members of the armed forces. In this prospective follow up study of a cohort population, a sample of 212 war injured survivors who agreed to participate in this study, were taken from a total of 234 Kuwaiti injured war survivors that has voluntarily registered in the Social Development Office (SDO) caring for war traumatized victims. The entire sample was approached in 1998. This was the cohort population that was re-tested in the second phase.

In 2003 the same sample was approached again for retesting. Of the original 212 subjects that were tested in 1998, (15) refused to participate in the study again. In addition, 54 of 212 cases could not be contacted because new telephone numbers were not available for them (54/212= 25.4%), and 19 cases were not eligible for retesting because they were travelling outside the country, were in prison, had severe disability or had died (19/212= 8.9%). Thus 123 cases were reassessed in 2003 with the addition of 33 new cases that were not examined in (1998) but were registered in SDO after the first assessment.

Participation in the study was voluntary and the subjects did not receive any monetary rewards for participating in the study. Participants were given the choice to withdraw from the study at any time during the study.

The following is the result of the response of the cohort sample for participating in the study (Table 1).

Table. 1. Study population in 2003 compared to 1998

Study Population	No. of cases		%
Assessed in 1998	212		90.5
Assessed in 2003 and in 1998	123		58
Refused	16/212		7.5
Not reached because contact could not be made	54/212		25.4
Long period travel out side the country	7	19/212	8.9
In prison	2		
Severe disability e.g. paralysis, end stage renal failure	3		
Died	7		
Total non reached cases 54 +19	73		34.4

4. A. Recruitment of the sample:

A trained contact officer that gave prepared explanatory introduction to the study contacted each participant. The participant was invited to participate in the study. If the participant agreed to participate in the study the following procedure was followed for both first and second assessment:

The contact officer followed and perused the following for contacting the participants:

1. Upon contacting a potential subject, the officer identified herself as the contact officer for this research study on the FGW-injured individuals in Kuwait, and she invited the participant to participate in the study.

2. All the participants were told the same massage that: “The principal investigator would like to meet you to study the possible consequences of the traumatic experiences you have gone through during the invasion and occupation period of Kuwait”. If she/he agreed the next step was followed.
3. The contact officer explained the procedures to be carried out at the appointment time. She gave a brief explanation about the questionnaires and scales. Also she explained to the participants that there will be a consent form which she/he will receive on arrival day to sign for accepting

participation in the study. Each participant was asked to bring any available medical records pertaining to his/her physical injury.

4. On the day prior to the appointment a phone call was made to confirm the appointment arrangements, and any clarifications the participants liked to have before coming to the interview.

4. B. Preparing the list

The list of the participants was obtained from the SDO after approval of the protocol of the study by the ethical committee at SDO (for the first phase of the study) and Department of Community Medicine and Behavioral Sciences in Faculty of Medicine of Kuwait University and Adelaide University (for the second phase of the study). All the injured in the list were approached. In the second phase an updated list was obtained from the SDO for the new address of the registered injured.

5. Interview Procedure:

All interviews were conducted in Arabic, and all questionnaires were Arabic versions of the questionnaires described. For the purposes of this dissertation, I have presented the English original of questionnaires if appropriate and English paraphrases of interview questions. Arabic versions of the materials are available from the author on request. The procedure lasted for an average of (3) hours for each participant and included an assessment of his/her physical injury, the administration of face to face scales and self-administered questionnaire

On arrival the principal investigator received the subject and explained the procedure. At this point the consent form was signed.

5. A. Informed Consent

Each subject was given an informed consent for participation in the study. The ethical committee of Kuwait University Medical College - Kuwait and Adelaide University-Australia, approved this research. The principal investigator at the face-to-face interview explained the purpose of the study and their role in the second part of the study. It was emphasized to the participants in the consent that they were involved in a research project and the information collected from the subjects would be confidential. That no information about any individual participating in the study would be given to others, including Military, Police, or National Guard forces. It was also stressed that the results of this study would be used for publications as articles in professional journals and the data would be statistically analysed in grouped format. It was also stressed that the identity of any individual would not be revealed in any publications or reports. The participants signed the consent form in the first as well as the second phase of the study.

5. B. Ethical Obligations:

For any medical conditions that needed clinical follow up investigation and /or treatment, a referral to the appropriate specialty for further follow up and therapy was made for the subject. The results of the medical examination were treated as a confidential document within the research study. The participants were provided with a copy of their medical examination results if they asked for it.

5. C. Data collection

This analysis was part of a large investigative study. Data collection was performed by the principal investigator and by psychologist and social worker interviewers. The interviewers had received four weeks of intensive training for the study, including 'practice interviews', before data collection with the presence of an observer to verify the procedure. They had interviewed all the adults of their own family at their homes individually for the first phase of the study in (1998). The participation in this study was voluntary no benefits (financial) were given to the participants.

5. C. 1. First Phase

The first phase of the project was conducted over a seven months period from November (1997) to May (1998). The second phase i.e. assessment of the project was carried out over eight months from February to September (2003).

At the first assessment all of registered Kuwaiti war-injured victims were approached, and of (234) individuals (212) war-injured subjects were studied, leading to a refusal rate of (9.5%). The causes of their injuries were due to combat or torture. The family members of these subjects were (467) adults and (203) children. All the participants were informed about the procedure. The principal investigator interviewed them for completion of trauma questionnaire and CAPS scale. The interview lasted 3 hours for each individual, using a general questionnaire and an injury questionnaire

Then a set of questionnaires and scales were applied for the diagnosis of PTSD and other possible associated psychiatric morbidity. The presence of current or lifetime PTSD as defined in DSM-IV was assessed using CAPS. In the first phase of the study in (1998), a visit was also made to war-injured home to interview the rest of family members: adults and children using questionnaires and scales as shown in the appendixes. Trained psychologist and social workers conducted the interview.

All the interviewers conducted 'practice interviews', before data collection with the presence of an observer to verify the interview procedure. The interviewers had interviewed all the non-injured adults and children of the family individually at their homes. They first applied the questionnaires, then the PTSD scale. The translated scales used in this study were used in a previous epidemiological study in Kuwait (Al-Hammadi et al 1994). An informed consent was taken from each head of family (household) by the interviewer before beginning of the interview with children. Family members were informed that the researchers were conducting a study to see what kinds of experiences the family may have had during the invasion and occupation period. The interviewers were checked by random selection of families who were called by principal investigator. The procedure for each child lasted average of (2) hours and included the rating scales.

5. C. 2. Second Phase:

In the second phase, the family members were not included in the re-assessment. The (212) war-injured subjects were approached for reassessment (Table 1) shows the fate of the sample tested in the first phase. The same steps followed in the first phase were repeated with additional steps in the second phase. A written informed consent was also obtained in this part of the study. The participants were given the results of there blood tests. Structured psychiatric interview, including demographics, history of thyroid disease, and concurrent medications, substance abuse, eating disorders, psychiatric past and present history were taken. The measurements of diastolic and systolic blood pressure were taken following the standard protocol recommended by WHO. New trauma history since the first assessment was also determined. Each subject underwent a detailed medical assessment; this assessment was conducted over an average of (3) hours for each participant.

Biochemical assessment of these subjects comprised serum cortisol, and thyroid-function tests including free serum thyroxine T4 (fT4), free triiodothyronine T3 (fT3) and Thyroid stimulating hormone (TSH). Questionnaires and scales applied in the first stage were applied in the second stage with the addition of Impact of Event Scale (IES) and Composite International Diagnostic Interview (CIDI). The CIDI is face-to-face interview instrument used to diagnose depression, anxiety, psychosis, obsessive-compulsive disorder, and alcohol and substance use disorders for research purposes based on ICD-10 criteria.

A Research Assistant was used in this phase of the study that had a bachelor degree in psychology. She was involved only in calling the clients and the arrangements required for the interview. The research assistant had the skills, experience and qualification to administer such instruments and to understand the stressful, unpleasant or upsetting memories or feeling of participants. She had been involved in an intensive training program that included lectures about the aim of the study, war and non-war Traumatic events, interview skills, ethics, and confidentiality, Posttraumatic stress disorder, and other psychiatric disorders such as Psychosomatic disorder, Depression, Anxiety and OCD.

6. Assessment

6. A. Standardized measurements

The medical examination involved the following tests:

6. A. 1. Pulse Rate (PR)

This was measured using a digital pulse recorder. The pulse was taken after the introductory phase of the study and signing the consent.

6. A. 2. Blood pressure (BP)

This was measured using a digital BP recorder in the sitting position using the right arm. The BP was taken after the introductory phase of the study and signing the consent.

6. A. 3. Waist-Hip Circumference WHP

This was measured using a standard measuring tape to measure the waist and hip circumference.

6. A. 4. Weight- Height: Body Mass Index (BMI)

This was calculated by measuring both the height, and weight using calibrated digital scale.

6. A. 5. Visual analogue scale (VAS) before the interview

This is a subjective assessment for each client. Each participant assessed in a scale of (5) the level of distress he was feeling: (1) no distress to (5) most severe distresses before starting the interview.

6. A. 6. Visual analogue scale (VAS) after the interview

This assessment was done at the end of the interview.

6. B. Biological measures

6. B. 1. Cortisol level

Blood samples (5 ml) in red-topped (untreated) vacuum tubes for cortisol hormone were collected between (9 and 11 am) from the participants. The analysis was performed at the main endocrinology lab at Mubark Al-Kabeer teaching Hospital – Kuwait University- Kuwait

To reduce the possibility that anxiety related to psychometric and medical assessments, cortisol samples were obtained immediately after explanation of the procedure and signing the informed consent before the potentially stress-inducing rating scales, and physiologic assessments. The samples then were sent to the lab where it were centrifuged for (2) min, and stored at (−20°C), cortisol levels later measured by radioimmunoassay methods. Plasma cortisol was measured using an antibody-coated tube radioimmunoassay (RIA).

6. B. 2. Thyroid function test: fT3, fT4, TSH

The thyroid functions were measured using (5) ml of the collected blood. The hormonal assay was used for this analysis. The blood samples for each participant were collected and, after setting of the clot and centrifugation, the serum was divided into three (1.5) ml aliquots in small plastic vials. Serum free T4, free T4, and thyroxin Stimulating hormone (TSH) concentrations were measured by radioimmunoassay (RIA) procedures with the use of RIA kits.

6. C. Trauma assessment

Trauma Questionnaire: type and extent of physical disability for injured victim. The trauma with further ranked in a score of 1-10 in respect of fear, helplessness, and horror. The traumas were ranked according to their severity.

Trauma Questionnaire included: type, extent of physical disability. The trauma was further ranked in a score according to the Kuwait Law ranking disability due injury. Appendix shows scoring of the questionnaire.

All participants were screened in the first assessment using this questionnaire for the extent of the traumatic events they sustained through during Kuwait invasion and occupation period.
All participants were screened for the extent of the traumatic events they sustained through during Kuwait invasion and occupation period. The set of objectively specified traumatic experiences was composed of the following variables:

A. Type and extent of physical injury using a trauma questionnaire.
B. A general rating questionnaire that included witnessing abusive violence, torture, execution, or they were forced to hide,
C. Arbitrary arrest, torture, humiliation and human rights violation,
D. Intense fears of war: deprivation, arrest, shooting, and
E. Combat exposure.

The questionnaire included detailed analysis of the possible types of trauma adults had gone through during the invasion and occupation period of Kuwait, and location of the subjects during the same period (See the Appendix).

6. D. Posttraumatic Stress Disorder (PTSD) Assessment

6. D. 1. Clinician Administered PTSD Scale CAPS (Blake et al 1990).

The participants gave brief Questionnaire before CAPS to determine types of trauma other than war related traumatic events that may be experiences.

CAPS is a structured clinical interview that provides a standardized method for making current and lifetime DSM-IV diagnosis of PTSD and for determining PTSD symptom severity. The CAPS has good test-retest reliability, internal consistency of the three symptom clusters: intrusion, avoidance and arousal.

Each symptom was rated according to frequency (0-4), intensity (0-4).

1. B: Re-experiencing: symptoms (4 items)
2. C: Avoidance: symptoms (7 items)
3. D: Arousal: symptoms (6 items)

The severity score intrusion (re-experiencing), avoidance and arousal were calculated as the sum of both frequency and intensity of each item endorsed.

PTSD diagnosis based on DSM criteria i.e. at least (1) of criterion B, (3) of criterion C and (2) of criterion D. For each symptom to be positive participant has to experience the symptoms at least once per month and the intensity of the symptom should be at least mild.

6. D. 2. Impact of Events Scale (IES-R):

This is a PTSD scale. Daniel S. Weiss and Charles R. Marmar developed the IES-R in (1997) using DSM criteria for PTSD. The original IES was developed in (Horowitz et al 1979) based on DSM-III. It is a self-report measure designed to assess current subjective PTSD symptoms. It consisted of (22) items in the revised copy. The participant was asked to rate each item in the scale: (0-not at all), (1-a little bit), (2-moderately), (3-quite a bit) and (4-extremely) according to the past (7) days.

Weiss and Marmar (1997) reported that the internal consistency of the (3) subscales was found to be very high, with intrusion alphas ranging from (.87 to .92), avoidance alphas ranging from (.84 to .86), and hyperarousal alphas ranging from (.79 to .90) (Briere 1997).

Weiss and Marmar noted that the hyperarousal subscale has good predictive validity with regard to trauma (Briere, 1997). The intrusion and avoidance subscales that are originally IES items had high endorsements of up to (85%) Horowitz et al (1979).

<u>Scoring Method:</u>

Avoidance Subscale:	Mean of items 5, 7, 8 11, 12, 13, 17, 22
Intrusions Subscale:	Mean of items 1, 2, 3, 6, 9, 14, 16, 20
Hyperarousal subscale:	Mean of items 4, 10, 15, 18, 19, 21

7. Scales and questionnaires

The participants were screened for the prevalence of other psychiatric disorders. The set of scales for these assessments included Symptoms Check List–90R, Impact of Event Scale, Eysenck Personality Inventory Scale, Life Events Scale and CIDI. The last scale was administered as face–to-face interviews while the first sets of scales were self-administered. Professional translators and back-translated into English to ensure that the Arabic versions were matching with the English ones translated these scales from English into Arabic. A panel of three Arabic-English speaking researchers resolved any discrepancies.

7. A. General Health Questionnaire

This questionnaire also included socio-demographic data such as age, gender, education history, and if it is affected by the disability, occupation history and if it is affected by the disability, marital status, and social history, developed specifically for FGW survivors traumatic experiences, life style factors (such as, smoking, alcohol, and substance abuse), current and past medical and psychiatric history, and prescribed medications. The questionnaire also had included a set of objectively specified traumatic experiences was composed of the following variables:

1. Witnessing abusive violence, torture, execution, or they were forced to hide
2. Arbitrary arrest, torture, humiliation and human rights violation,
3. Physical injury, bullets, shells,
4. Intense fears of war: deprivation, arrest, shooting, and
5. Combat exposure.

7. B. Symptom Checklist – 90 Revised (SCL-90-R) Derogatis et al (1994).

Symptom Check-list – 90 Revised: SCL-90-R, Derogatis et al (1994).

7. C. Eysenck Personality Questionnaire – EPQ Eysenck et al (1975).

Eysenck Personality Questionnaire – EPQ (Eysenck et al 1975). It in volves :
- Extraversion/Introversion:
- Neuroticism/Stability:
- Psychoticism/Socializations:
Each symptom was scored 0-1.

7. D. Life Event Scale (LES) (Holmes et al 1967).

This scale was created by Holmes et al (1967), it includes 46 life events that participants may gone through one year prior to the interview. A score ≥300 points is considered as signifies significant stressful events experienced by the participant in the one year prior to the assessment.

7. E. CIDI (World Health Organization 1993).

CIDI: is a face-to-face structured interview instrument used to diagnose mental disorders including PTSD, depression, anxiety, psychosis, obsessive-compulsive disorder, and alcohol and substance use disorders for research purposes based on ICD-10 criteria.

7. F. GW Syndrome (GWS)

This questionnaire was adopted from Adelaide University for the assessment of FGW syndrome.

8. Data Handling and Management

The data collected from the medical interview were kept in the file of each subject and were treated confidentially with the rest of the family members data collected in the first stage. At the end of the project these files were kept confidentially in Department of Community Medicine and Behavioral Sciences at Faculty of Medicine of Kuwait University.

8. A. Procedure

Data were collected separately for each questionnaire and scale. Cortisol level and thyroid functions were analyzed at the Endocrine Laboratory at Mubarak AlKabeer Hospital.

8. B. Checking processing coding

Taking random questionnaires and checking data entry checked data entry. This procedure was done to verify data entry by taking random questionnaire or a rating scale and follow the data entry.

8. C. Data Entry

A data entry person was hired for this purpose. He had a university BA degree in computer science and accounting.

8. D. Storage

After data entry the study questionnaires and scales were stored at Department of Community Medicine and Behavioral Sciences at Faculty of Medicine – Kuwait University.

8. E. Statistical analysis

Data entry program using Statistical Package for Social Scientists (SPSS) was used to enter data. Data entry was executed parallel to the data collection. The data were analysed using SPSS. Thyroid measures included were fT3 pmol/l (equivalent to 1.54 pg/ml), fT4: pmol/l (equivalent to 12.87ng/dl) and TSH: IU/l. These were included in a one-factor multivariate analysis of variance to determine whether there were overall mean differences between PTSD and non-PTSD groups when all dependent variables were considered simultaneously. Independent chi square tests were used to determine group equivalence for clinical and demographic variables.

The thyroid functions were classified as follows:

1. fT3: Low Normal (LN) ≤ 3.6pmol/l (2.33 pg/ml),
Normal (N) 3.61~4.89pmol/l (2.34- 3.17pg/ml),
High Normal (HN) > 4.89 pmol/l (3.17pg/ml)

2. fT4: Low Normal (LN) ≤13.12pmol/l (168.85ng/dl),
Normal (N) 13.12~19.34pmol/l (168.85-248.9 ng/dl),
High Normal (HN) >19.34pmol/l (>248.91ng/dl).

3. TSH: Low Normal (LN) (≤0.74),
Normal (N) (0.741~2.20),
High Normal (HN) (2.201~5)

9. Research Supervisors

9. A. Research approval

This research was approved by the ethical and research committee at SDO. It was also approved by Department of Community Medicine and Behavioral Sciences at Faculty of Medicine – Kuwait University.

9. B. Local supervisor

Dr. Jaafar Behbehani PhD, Department of Community Medicine and Behavioral Sciences at Faculty of Medicine – Kuwait University.

9. C. Main supervisor

Prof. Alexander McFarlane, Head of Psychiatry Department Adelaide University.

Chapter IV. Chronic Posttraumatic Stress Disorder

1. A. Introduction:

Post- traumatic stress disorder (PTSD) is defined in the DSM-IV APA (2000) as a disorder with a group of symptoms related to anxiety disorder. Two important factors in the development of PTSD are trauma of sufficient severity and the person's response to the trauma. This disorder was seen and described after World Wars I, and II, and it was given different names earlier. PTSD is a common worldwide disorder more prevalent in populations that suffered from war and terrorism. The symptoms of PTSD typically persist for several years and are accompanied by significant social and work impairment and co-morbid mental disorders. PTSD has also been described after non-conflict trauma, such as car accidents, rape, arrest and torture, burns, and industrial explosions. In addition, PTSD has been reported to be associated with natural disasters. The following are characteristics of a trauma that make it capable of causing the changes in the perception of an individual to lead to PTSD: a serious threat to one's life, physical integrity, one's family, a sudden destruction of one's home or community, or seeing another person who has recently been seriously injured or killed. Brunello et. al. (2001) indicated that epidemiological studies clearly indicate that PTSD has become a major health concern worldwide even if still poorly recognized and not well treated. Moreover he stated that PTSD comorbid with other psychiatric disorders such as major depressive disorders, anxiety disorders and substance abuse. He described PTSD (as in DSM-IV) that it provokes significant occupational, psychiatric, medical and psychosocial disability, and its consequences are enormously costly, not only to the survivors and their families, but also to the health care system and society and work impairment associated with PTSD is very similar to the amount of work impairment associated with major depression.

In this chapter there will be an explanation of the prevalence of PTSD and in this context the course of the condition after different stressors will be discussed. In this context the various risk factors and the nature of the Pathophysiology of PTSD will be outlined. These factors are relevant to considering what influences the course and nature of the condition. A secondary issue that requires consideration is the presence of co morbid psychiatric conditions that are frequently noted to be present in PTSD. These issues will be also assessed in the context of a description of the risk factors that appear to predict chronic PTSD in contrast to those patients who are likely to go into remission. This literature is of particular relevance to this study as the population being examined was assessed in the second phase of this study some 13 years after their trauma exposure.

In order to examine the factors associated with chronic PTSD in an Arab context, we present the results of a five-year (1998 – 2003) follow-up study of Kuwaitis who were physically injured during the (1990/91) Gulf war. The sample was taken from the registered war injured survivors in Kuwait after the Gulf war of (1990-1991).

1. B. PTSD Classification:

Posttraumatic stress disorder (PTSD) is a disabling condition almost universally associated with psychiatric comorbidity, reduced quality of life, and a chronic, often lifelong, course Davidson (2004-a). Four main subtypes of PTSD were classified based on the onset and duration of symptoms as grouped in DSM-IV, American Psychiatric Association (1994), fulfilling PTSD criteria, and the duration of these symptoms. DSM-IV defines chronic PTSD as that lasting longer than 3 months. The following are the four main types of PTSD:

1. Acute PTSD: Early onset, early resolution (duration of symptoms less than (3) months)
2. Chronic PTSD: Early onset, prolonged course (duration of symptoms is (3) months or more)
3. Delayed PTSD: Onset of symptoms after first 6 months of the traumatic incident.
4. Delayed and Chronic PTSD: Although not delineated in DSM III and IV, this is another logical subtype in which the patient has delayed onset of symptoms ((6) months after the traumatic event) and has already manifested PTSD symptoms for a period of greater than 6 months prior to diagnosis.

After first exposure to trauma some individuals will develop PTSD, which mostly dissipate within a short time. In some of these individuals symptoms will evolve into chronic and persistent PTSD. Chronic PTSD was further classified into subtypes. Schnurr (2003) studied 530 Vietnam Veterans and found that 30.6% had full lifetime PTSD, 14.5% partial lifetime PTSD, 14.7% full delayed PTSD, and 7.7% had partial delayed PTSD. When cluster analysis was performed for 223 veterans with full or partial lifetime PTSD 4 clusters of chronic PTSD could be identified: remitted (17.9%), chronic late onset (9.4%), chronic intermittent (23.8%), and chronic unremitted (48.9%).

Voloshin et al (2004) classified chronic PTSD according to the comorbid disorders. Chronic PTSD can present with comorbid states which will give this disorder more symptoms on presentation and the PTSD will probably be misdiagnosed as the comorbid state. Chronic PTSD was classified by Voloshin (2004) as: Chronic PTSD with depression, chronic PTSD with alcoholism and /or substance abuse, Chronic PTSD with OCD, Chronic PTSD with personality disorder, and so on. In his study of 165 combat veterans he could identify 4 chronic PTSD with depression sub types: anxious (36.6%), dysphoric (26.1%), apathic (20%) and somatoform (17.7%).

Seedat (2003) proposed that chronic PTSD has a sub type with psychosis. In these patients the presence of psychosis that coexists with PTSD is associated with negative family histories of psychosis. In Seedat (2003) dopamine beta-hydroxylase (DβH) a neurotransmitter was proposed to differentiate psychotic from nonpsychotic subtypes of PTSD. Significantly higher levels of DβH activity have been measured in patients with PTSD plus psychosis compared with PTSD patients minus psychosis. This finding suggests that high DβH activity may be a risk factor for the psychotic subtype. In contrast, low DβH levels have been implicated in adults with psychotic depression Meltzer et al., (1976), and familial paranoid schizophrenia Markianos et al., (1990).

1. C. Prevalence of PTSD:

Delayed onset PTSD is estimated to be 22% among combat veterans Kessler et al (1995). While chronic PTSD which lasts for more than 3 months is much more prevalent it was found that 52% of clients with lifetime PTSD had a form of chronic PTSD Kessler et al (1995). One third of the sample in this study continued to have PTSD symptoms. No span or limits have been defined for to what extent PTSD can go in time. In another study on WW-II POWs (18%) had chronic PTSD symptoms and (29%) had PTSD of about 5 years, Port et al (2001). The same was found by Zeiss & Dickman (1989) that (24%) were still having continuous PTSD symptoms and (62%) had an intermittent course. Furthermore they also found that (22%) of WW-II resistance fighters in Germany still had a chronic progressive course of PTSD.

Longitudinal prospective studies on PTSD in traffic accident victims have reported a (47%) to (53%) chance of still suffering from PTSD after a 3-year interval Koren et al (2001); Mayou et al (2002). PTSD endured over time and can persist for more than (12) years post trauma in war-traumatized youth Sack et al., (1999). Based on retrospective data from epidemiologic surveys, it has been estimated that the median time to remit from PTSD is (24.9) months Breslau et al., (1998), and that at least a third of subjects with PTSD never remit, independent of treatment Kessler et al., (1995).

Lifetime prevalence rates of PTSD are (10%) for women and (5%) for men as suggested by Kessler et al., (1995). About 12% of patients with sub-syndromal PTSD are seen by primary care physicians Stein et al., (2000). Dirkzwager et al., (2001);Green et al., (1992); Kilpatrick et al., (1987) concluded in their studies that war Survivors meet criteria for PTSD several years after the trauma, which suggests a lifetime pattern of PTSD .

Kessler et al (1995) estimated that the lifetime prevalence of PTSD is 7.8 %. Women had a higher prevalence than men 10.4% versus 5% respectively. The difference in the rates between males and females indicates that women are more prone to develop PTSD than males, Foa et al (2000), Breslau et al (1999). This also can be explained as females have a greater exposure of high-impact trauma (Rapes, sexual molestation, childhood neglect and childhood physical abuse) and a greater likelihood of developing PTSD when exposed to a traumatic event.

PTSD is more prevalent among war veterans than among any other group, and especially in those with physical injury. The National Vietnam Veterans Readjustment Survey reports that approximately 25% of U.S. veterans, men and women, were suffering from PTSD in the early (1990s) Foa et al (2000), Breslau et al (1999). Men with PTSD identify combat and witnessing someone else's injury or death most often as the cause of their condition. Women identify physical attack or threat most often as the cause of their PTSD. Someone with PTSD is at risk for developing other mental health disorders such as panic disorder, phobias, major depressive disorder, and obsessive-compulsive disorder. Substance use and somatization were also found to be common. The difference in the rates between males and females indicates that women are more prone to develop PTSD than males.

The Composite International Diagnostic Interview (CIDI) was administered to a representative national sample of 5877 persons aged 15 to 54 years in the part II sub-sample of the National Comorbidity Survey Kessler et al. (1995). It was found that the estimated lifetime prevalence of PTSD was 7.8%. Prevalence is elevated among women and the previously married. The traumas most commonly associated with PTSD are combat exposure and witnessing among men and rape and sexual molestation among women. PTSD is strongly co-morbid with other lifetime DSM-III-R disorders. Survival analysis shows that more than one third of people with an index episode of PTSD fail to recover even after many years. They conclude that PTSD is more prevalent than previously believed, and is often persistent.

The rates of PTSD across these studies could be attributed to different methodology (sample selection, inclusion and exclusion criteria, tools), types and degree of trauma exposure, degree of combat in veterans studies, duration of trauma, and time taken to the assessment and diagnosis, randomization and other factors such as past psychiatric histories and the presence of other physical and psychosocial co-morbidities.

1. D. PTSD Pathophysiology:

The direction to which PTSD takes in an individual after a traumatic event (i.e. whether acute, chronic, relapsing or late onset) depends on the following factors:

1. Genetic: Segman (2003) proposed that PTSD may follow a chronic course, and although exposure to a traumatic event constitutes a necessary requirement for diagnosis, but it is not a sufficient factor. Rather there is a significant genetic contribution, with an underlying genotypic vulnerability to this disorder that is only expressed following exposure to trauma.

2. Life Events: Persistence of the symptoms could be related to events that occurred during and after the trauma. In a study of Vietnam veterans, Schnurr (2004) examined 68 women and 414 men. He found that the development of PTSD was related to pre-military, military, and post-military factors. The maintenance of PTSD (failure to recover) was related primarily to military and post-military factors which involved life events.

3. Autonomic and hypothalamic-pituitary-adrenal HPA axis responses: Davidson (2004-b) suggested that following a trauma a certain proportion of the survivors will evolve into chronic and persistent type of PTSD. A number of factors increase the likelihood of this occurring, including characteristic autonomic and hypothalamic-pituitary-adrenal axis responses, co-morbid depression, especially in the form of somatization.

The etiology of PTSD remains not well defined, it may involve complex interactions of many factors such as: the magnitude of the stress after the trauma, genetic, psychological vulnerability of the person, perception of the threat, and the long-term biological and behavioral responses to the stress, Yehuda (2002). The psychobiology of PTSD patients during the course of the illness is different from those patients with acute stress reaction Yehuda (2002). The biological and cognitive mechanisms occurring shortly after trauma exposure mediate long-term symptoms observed in PTSD. Yehuda (1999) suggested that in PTSD there appears to be a failure of normal adaptive responses to contain and resolve the psychological and autonomic responses to acute stress. Moreover the overwhelming fear, horror, autonomic arousal and emotions such as guilt and anger may lead patients to avoid thinking about the traumatic event and thus impair psychological resolution and the development of effective coping mechanisms Yehuda (1999). Other factor proposed by Yehuda (1999) that may affect the biologic responses to a trauma includes the event, the inherited (genetic) background of the traumatized person, and environmental factors.

The two major affected structures in the brain namely amygdala and the hippocampus were shown by studies of PTSD patient using functional Magnetic Resonance Imaging (MRI) to have reduced hippocampal volume and by PET scan to have reduced blood flow in the middle temporal cortex Bryant et al (2003-a). The changes in these structures as suggested by Bryant et al (2003-a) were in the form of (1) an increase in the reactivity of amygdala (delay in the extinction of fear responses to reminders of the traumatic event) and the anterior paralimbic region, (2) a decrease in the anterior cingulated and orbitofrontal region, (3) the intrusive re-experiencing of symptoms are due to changes in the hippocampus (enhanced reactivity to stimulation and deficits in autobiographical memory).

Several neurotransmitter systems seem to be dysregulated in PTSD and these can be summarized as follows, Charney et al, (1993) and Yehuda, (1998-a,b):

1. Sensitization of the noradrenergic system - in particular alpha 2 adrenergic receptors causing increased levels of noradrenaline and enhanced Locus Coeruleus activity, explaining in part symptoms of autonomic hyperarousal and re-experiencing through the effects of beta adrenergic receptors in the amygdalae and cortical structures.

2. Serotonin controls the function of septohippocampal behavioral inhibition system. Sensitization of the serotonergic system would lead to hyperarousal symptoms.

3. Endogenous opiates have been suspected to mediate the symptoms of emotional numbing and amnesia.

4. High levels of corticotrophin releasing factor (CRF) in the cerebrospinal fluid, will lead to an enhanced plasma adrenaline and noradrenaline concentration and the consequent anxiety and fear related behavior.

Increased activation of the sympathetic nervous system was seen due to fear conditioning and progressive neural sensitization in the period post-trauma period Pitman et al (2000) and Kolb (1987). Le Doux et al (1988) proposed that the initial traumatic stimuli are associated with arousal and this serves as conditioned stimuli to trigger further arousal. This mechanism can be possibly be explained the fact that it involves repetitive activation by trauma reminders that elevate sensitivity of limbic networks Post et al (1995), reduce extinction of conditioned fear responses Charney et al (1993), or cause sensitization of the hypothalamic-pituitary-axis in which reduced cortisol fails to contain sympathetic activity, Yehuda (1997).

McFarlane et al (1997), Delahanty et al (2000) found that lower cortisol levels shortly after motor vehicle accidents were a better predictor of PTSD outcome at posttrauma than acute psychological indicators. Consistent with the proposition that the increased sympathetic activation in the acute phase of PTSD development is associated with subsequent PTSD, there is also evidence that resting heart rates of trauma survivors in the initial week after trauma are higher in those who later develop PTSD than those who do not, Bryant et al (2000) and Shalev et al (1998). But these findings were not replicated by Blanchard et al (2002). The level of cortisol

in patients with PTSD may not follow the known pattern that is seen in patients with other types with stress disorder, in which both the cortisol and the corticotropin releasing factor levels are high as observed by Baker (2005). Mason et al (1986) and Yehuda et al (1995) reported that cortisol level was low in patients with chronic PTSD with paradoxically higher levels of corticotropin-releasing factor in cerebrospinal fluid. It was reported by many studies Goenjian et al (1996), Yehuda (1993), that PTSD patients have an increased sensitivity of the negative feedback HPA with exaggerated suppression of cortisol level dexamethasone suppression test.

Delahanty et al (2000) and McFarlane (1997) suggested that the psychobiologic hypothesis of PTSD development indicates that the initial stressor initiates a series of continuous biologic events in the form of attenuated increase in cortisol levels. This was also evident by a higher heart rate indicating an activation of the sympathetic nervous system Shalev (1998). In the contrary, Pacak et al (1995) and Jeong (2000) reported that a decreased cortisol levels at the time of the trauma could prolong the availability of norepinephrine to synapses in both the periphery and the brain, which in turn might affect the consolidation of the memory of the incident. With this low "cortisol adrenergic activation" trauma will be strongly encoded, as proposed by Cahill et al (1994) along with distress, perceptual and coping effects which will delay recovery from the trauma and trigger a series of secondary biologic changes that consequently produce PTSD.

Chronic stress brought by continuous recollections of the event alters the structure and function of the brain's limbic system (hippocampus, amygdala, and hypothalamus) and the hypothalamic-pituitary-adrenal (HPA) axis Friedman et al (2002). Friedman et al (2002) suggested that the smaller hippocampal volume is hypothesized to be secondary to the damaging effects of stress on hippocampal neurons, possibly mediated through high levels of cortisol released during stress. The resultant stress-induced atrophy of neurons alters the processing of memory and may be responsible for the unwanted recollections of the traumatic event. Positron emission tomography (PET) scans of the brains of veterans with PTSD demonstrate increased activity in the amygdala when exposed to combat movies, Rauch et al (1996), which he thinks may be responsible for the anxiety and fear response. Brain imaging studies also demonstrate altered levels of activity in the hypothalamus, an integral component of the HPA axis. This change in activity was examined by Rauch et al (2000) and Ehlert et al (2001). They found that the changes in the hypothalamic activity level modifies the amount of corticotropin releasing factor (CRF) secreted by the hypothalamus, thereby modifying the function of the pituitary gland because of the rich neuronal connections between these two structures. Alterations in pituitary gland function affect the

adrenal gland resulting in increased levels of norepinephrine and epinephrine (as evidenced by the levels of their metabolic by-products in 24-hour urine specimens) and consequently physiological hyperarousal manifested by an elevated blood pressure, increased heart rate, and increased sweating.

McEwen et al (2001), described the damaging actions of adrenal glucocorticoids (secreted during chronic stress) as "allostatic load", describing the adaptation to adverse conditions. Adrenal steroids display both protective and damaging effects in the hippocampus. These steroids biphasically (1) modulate the excitability of hippocampal neurons, and the high glucocorticoid levels and (2) severe acute stress impair declarative memory in a reversible manner. McEwen et al (2001) hypothesized that structural plasticity in response to repeated stress starts out as an adaptive and protective response, but ends up as damage if the imbalance in the regulation of the key mediators is not resolved, this will results in chronicity in PTSD. Furthermore they suggested that the morphological rearrangements in the hippocampus brought on by various types of allostatic load alter the manner in which the hippocampus participates in memory functions and it is conceivable that these may also have a role in chronic pain perception. McEwen et al (2001) described three types of plasticity in the hippocampal formation in which adrenal steroids play a role:

First, adrenal steroids reversibly and biphasically modulate excitability of hippocampal neurons and influence the magnitude of long-term potentiation, as well as producing long-term depression.

Second, adrenal steroids participate along with excitatory amino acids in regulating neurogenesis of the dentate gyrus granule neuron, in which acute stressful experiences can suppress the ongoing neurogenesis.

Third, adrenal steroids participate along with excitatory amino acids in a reversible stress-induced remodeling of dendrites in the CA3 region of hippocampus of male rats and tree shrews, a process that affects only the apical dendrites and results in cognitive impairment in the learning of spatial and short-term memory tasks.

1. E. Chronic PTSD:

PTSD is a persistent disorder among trauma survivors with relatively good evidence supporting that from the literature. Research suggests that survivors of assault, man-made disasters, and combat frequently meet criteria for PTSD even several years after the original trauma Dirkzwager et al (2001). After varying periods of time, two samples of Dutch aging military veterans: 576 veterans with a military disability pension and 198 community sample veterans, who fought in World War II, the former Dutch East Indies, and Korea. Both samples were investigated in (1992) and in (1998) with a standardized and validated instrument measuring PTSD symptoms. In 1992, (27%) of the veterans with a military disability pension met the criteria for a PTSD diagnosis; in 1998, this was (29%). Of the community sample veterans, (9%) reported a PTSD diagnosis in 1992; in 1998 this was (8%). This was not related to aging. In this study the rate of PTSD did not change with time for war survivors.

Green et al (1992) examined a total of 193 subjects exposed to the Buffalo Creek dam collapse of 1972, (14) years after the tragedy using diagnoses derived from the Structured Clinical Interview for DSM-III (SCID). Past and present PTSD was found in a significant portion of the sample. Major depression was the next most common diagnosis and was highly related to PTSD. Anxiety disorders were also common. The overlap with other diagnoses was quite similar to that found in a sample of Vietnam veterans, except that the natural disaster sample had fewer dysthymic disorders, substance abusers, and antisocial personality disorders.

Events which cause PTSD are significantly more numerous than specified in diagnostic and statistical manual IV (Waddington et al 2003). They proposed another name for the PTSD they called it Prolonged Duress Stress Disorder (PDSD), as the existence of criterion A is not a necessary prerequisite in establishing a diagnosis of PTSD, because PTSD can occur after medical events such as giving birth, miscarriage, heart attack, cancer, or hospitalization following resuscitation may give rise to PTSD. Further, people experiencing prolonged periods of distress may equally develop a post-traumatic syndrome without any particular event having occurred to surpass their defenses.

Longitudinal prospective studies on PTSD in traffic accident victims have reported a 47% to 53% chance of PTSD after a 3-year interval, Koren et al., (2001); and Mayou et al., (2002). A 12-year follow-up study by Sack et al., (1999) demonstrated that PTSD endured over time in war-traumatized youth. Twenty-seven of 40 Khmer adolescent youths who had survived the horrors of the Pol Pot regime (1975-1979) as children and 4 of 6 who had escaped this war were re-interviewed for the fourth time, during the summer of 1996, to determine their diagnostic status for posttraumatic stress disorder (PTSD) and/or depression and their functional status with regard to occupational and/or educational pursuits. They had been interviewed initially in 1983-1984 and again 3 years`(1987) and 6 years (1990-1991) later. It was found that PTSD prevalence rates were comparable to those found 6 years earlier, and rates of depression were much lower but had increased somewhat over the ensuing 6 years. The onset of PTSD was quite variable, with 18% of subjects (7/40) developing PTSD at least 5 years after cessation of the Pol Pot hostilities. Most subjects were functioning well, regardless of diagnostic status.

1. F. Course of PTSD

PTSD is a chronic disorder with a relapsing course Erickson et al. (2001). Chronic PTSD was also found in studies of second Gulf war veterans McFarlane et al (1992). For studying the natural course of chronic PTSD Perkonigg et al (2005) in a prospective, longitudinal epidemiological study followed 2,548 of individuals from the general population 14-24 years in Munich, Germany. Out of these 125 of them who had PTSD were followed for 34–50 months. The author found the following course chronic PTSD may take: 52% remitted, 48% no significant remission and those with chronic PTSD were more likely to have higher rates of avoidant symptoms.

The NVVRS, Schlenger et al (1992) showed that majority of veterans successfully readjusted after war, while a minority of them were suffering from psychological problems such as social and work difficulties. In this study the prevalence of acute PTSD in combat veterans was 15.2% for males and 8.5% for females; and for life time PTSD 30.9% for males and 26.9% for females. With higher exposure PTSD was 35.8% for males and 17.5% for females. In 1995 Kessler reported the PTSD in the national Comorbidity survey on the general population epidemiology to a representative national sample of 5877 persons aged 15 to 54 years. They found that the estimated lifetime prevalence of PTSD is 7.8%. The National Vietnam Veterans Readjustment Study (NVVRS) estimated the lifetime prevalence of PTSD to be 30.9% among male theater

veterans, 26% among females; lifetime prevalence of partial PTSD was an additional 22.5% and 21.2%, respectively; delayed prevalence of partial PTSD was 11.1% in males and 7.8% in females, Weiss et al (1992). NVVRS findings indicate that of the 1.7 million veterans who ever experienced significant symptoms of PTSD after the Vietnam War, approximately 830,000 (49%) still experience clinically significant distress and disability from symptoms of PTSD. The contribution of partial PTSD represents an estimated additional 350,000 veterans. In the same study O'Toole (1996) indicated that in the same study NVVRS out of a group of 406 Vietnam veterans exposed to high combat war-zone stress, compared with the non-combat group of 783 there were significantly more likely to have all psychological diagnoses to be more frequently than in the low or moderately exposed individuals and their rates of delayed PTSD were also elevated at 35.8%. In addition he attributed the methodological difference in rating PTSD to explain the above PTSD rated and the rates reported by the Center Disease Control (CDC) where they found lifetime prevalence of 16.5% (of which 14.7% was combat related and 1.8% non-combat) and delayed (one-month) prevalence of 2.2%, and for the non-Vietnam veteran lifetime rate of 3.2%.

O'Toole et al (1996) examined a simple random sample of 1000 male Australian Vietnam veterans they found that: 59.8% had at least one lifetime disorder in diagnostic interview schedule (DIS), 33.3% had at least one delayed disorder in the DIS, delayed PTSD 11.6%, lifetime PTSD 20.9%, 36.6% were having no disorder, 2.6% only PTSD, 17.3% PTSD with co morbid disorder, 82.7% of lifetime PTSD had additional lifetime DIS, 28.9% of lifetime DIS had PTSD.

Type of PTSD is the most important determinant of the course of this disorder in any traumatized patient; Johnson et al (2004) proposed the following course of PTSD patients:

(1) Acute onset PTSD has: better response to treatment, better prognosis (i.e., less severe symptoms), fewer associated symptoms or complications, and the symptoms would resolved within (6) months,

(2) About (50%) of those who have acute onset of symptoms recover within (6) months,

(3) (30%) develop chronic symptoms that may affect them for the rest of their lives.

(4) Others experience intermittent periods of symptom severity and remission,
(5) In the delayed onset PTSD it is associated with chronicity of PTSD disorder or symptoms, possible repressed memories, with worse prognosis.

In his (6) years follow up longitudinal study of (51) treatment-seeking male veterans with combat-related PTSD Johnson et al (2004), assessed the association between PTSD and other psychiatric symptomatology, social functioning, at (18) months, and (6) years. The results showed an extremely high mortality rate of (17%) over (6) years. The remaining veterans showed improvement in violence and alcohol and drug use, but an increase in hyperarousal symptoms and social isolation. Nearly three-fourths had had an inpatient hospitalization. Results indicate that the majority of the veteran sample had experienced some improvement in their ability to cope with their chronic illness, decreasing their use of violence and substance abuse but still were experiencing high levels of symptomatology. The extremely high mortality rate, however, provides a somber reminder of the seriousness of this disorder.

Waddington et al (2003), proposed a "cascade" concept for PTSD which involves an independent entity for PTSD which offers, with time, different symptomatic appearances, in evolution, because of events caused by after effects, in different areas of the PTSD itself. All of these concepts outline the transnosologic appearance of the PTSD which makes it hardly recognizable. Waddington (2003) stressed on the crucial nature of early detection of PTSD since the greater the time elapsed the more difficult it becomes due to the evolutionary aspect of the syndrome, which initially has more readily recognizable symptoms. The consequences of an unrecognized PTSD are serious and affect both the individual and his immediate family and friends, contributing further to the aggravation of the problems.

1. G. Chronic PTSD co-morbidity

PTSD frequently presents with co-morbid mental disorders that can complicate it as suggested by Erickson et al. (2001). McFarlane (2000), and McFarlane and Yehuda, (1996), proposed a multistage model for the pathogenesis and maintenance of the psychopathology of chronic PTSD, in which the modulation of the acute response may determine long-term outcome of the chronic disorder. In the first stage of this model, PTSD develops when a person is unable to create a sense of safety and control during the early stress response. In the second stage, the person’s adaptation to the chronic symptomatic state of PTSD will determine further

psychological consequences of trauma. If the person is unable to cope effectively with the emotional and interpersonal disruption associated with PTSD symptoms, other psychiatric disturbances develop.

Simon et al (1999) defined somatization as: a condition with somatic symptoms of major depressive disorder, medically unexplained symptoms of depressive disorder, and denial of psychological symptoms of depression in the presence of significant levels of somatic distress. They found that 85% of patients with major depression met at least one of these definitions which somatized depression.

Somatization is one of the co-morbid disorders that is encountered in PTSD as it was described in the following literature. Zatzick et al (2003) raised the association between the physical symptoms and PTSD. Solomon et al, (1987) showed that the physical symptoms are correlated with the levels of psychological distress in Israeli soldiers up 2 years after the trauma. Andreski et al, (1998) conducted a prospective study on 1007 patients with PTSD; he found that individuals with PTSD were more likely to develop somatization disorder. Katon (1991) indicated that there is a near linear relationship between the number of somatic symptoms, and the number of delayed and past psychological symptoms such as anxiety and depression. In another study Katon et al, (2001) has suggested that somatic symptoms may serve as proxy measures of psychological distress and cognitive impairment. Fatigue is one symptom that is related to somatization and associated with psychological disorders Rucci et al, (2003). Simon et al (1999) demonstrated that 45% and 95% of patients with depression had somatic symptoms using World Health Organization data collected in primary care centers in fourteen countries.

Davidson et al (2004-a) highlight those patients with PTSD who present in primary care are likely to present with a range of somatic symptoms. This could be due to the reason given by Kessler et al (1995) in the National Comorbidity Study that 62% of these patients did not believe they had a problem, inspite of having quite severe impairment. Beckham et al (1998) identified PTSD symptoms corresponded to the physician rated health problems and were significantly correlated in the self-report measures, and this could explain their treatment seeking behavior. Rona et al (2006) examined the relationship between psychological symptoms, and physical health in the British Armed Forces who found that although 12.4% of them reported physical symptoms, few gave psychological reasons for this as predominant reason for this was chronic physical injury. In this study it was indicated that these patients tend to ignore the link between the psychological symptoms and the physical disability, and this may explain why they do not

seek psychological treatment. McCarroll et al (2002) studied prospectively mortuary workers in the first Gulf War who found that they had significantly increased levels of somatic symptoms in those with intrusion in avoidance symptoms. It is concluded that it is highly probable that when these individuals become unwell, are likely to present with these symptoms rather than those of a psychological nature alone.

To assess the prevalence of anxiety disorders in Gulf War veterans, Black et al (2004-a) examined 4886 military personnel through a telephone interview, and compared them to a population-based sample of 4886 military personnel they found that 163 (3.7%) had at lease one of three anxiety disorder: (76 panic disorder, 108 general anxiety disorder, 53 PTSD). Depressive disorders were also reported by Black et al (2004-b), 192 (32%) of the 602 surveyed veterans had delayed or lifetime depressive disorders: major depression, dysthymia, depressive disorder not otherwise specified. The following psychiatric co morbid disorders were found in depressed deployed veterans vs. depressed non-deployed veterans: cognitive dysfunction (55% vs. 35%), anxiety disorders (59% vs. 33%), specific phobias (12% vs. 2%), PTSD (33% vs. 10%), and Lifetime substance use disorders (70% vs. 52%), alcohol disorders (68% vs. 52%).

Chronic psychiatric consequences of disaster were studied by Favaro (2004) on (39) survivors, (36) years after the Vajont disaster. He found that lifetime frequency of full PTSD was (26%), and a further (33%) of the sample displayed partial PTSD. Lifetime major depressive disorder (MDD) was present in (28%) of the subjects. The factors that predicted MDD were female gender and number of first-degree relatives lost in the disaster.

The mean BMI in male veterans was 30.3 ± 5.6 Kg/m², 38.2% of the veterans were overweight, 40.1% were obese and 6.4% were morbidly obese this was based on a study of 157 American veterans with PTSD Vieweg et al (2006). In a sample of 2425 male American veterans Spiro et al (2006) studied the health status of individuals with PTSD. PTSD prevalence was 20.2% in the sample, 24.3% among those exposed to traumatic events 15.5% had depression but not PTSD. He found that the health status of individuals with PTSD and/or depression was significantly worse than that of patients with neither disorder.

In a descriptive study Hopper et al (2006), investigated the relationships between parasympathetic activity and baseline heart rate (BHR) in 59 adults (50 females) with PTSD. To reach to this they studied the basal respiratory sinus arrhythmia (RSA), which is a measure of

parasympathetic cardiac activity, which negatively correlated with basal HR. He found that a substantial proportion of those with PTSD may not have elevated BHR suggesting a parasympathetic contribution to basal HR in PTSD. Beckham et al (2003) also failed to find BHR differences between veterans with PTSD and combat-exposed controls. Hopper et al (2006) indicated that "there are three major reasons to study parasympathetic contributions to BHR PTSD: First, the parasympathetic branch of the autonomic nervous system influences HR, including resting HR, independently of the sympathetic branch, Second, parasympathetic activity makes a greater contribution to HR than sympathetic activity; the parasympathetic branch exerts a much wider range of cardiac chronotropic control than the sympathetic branch, on the order of 7:1 in humans, Third, abnormally low tonic parasympathetic activity on the heart has been implicated in cardiovascular disease and hypertension, including lethal arrhythmias, atherosclerotic coronary artery disease, congestive heart failure, and sudden death in coronary artery disease". Buckley et al (2001) in a Meta analysis study for the resting cardiovascular functions in PTSD indicated that individuals with a delayed PTSD diagnosis have higher resting HR relative to both trauma-exposed individuals without a PTSD diagnosis and non–trauma-exposed individuals. The effect sizes for comparisons on basal HR were greatest in studies with the most chronic PTSD samples. He stated that "if repeated cardiovascular reactivity to stress accounts for the relationship between PTSD and elevated basal cardiovascular activity, one would expect the probability of HR and blood pressure elevations to increase along with the chronicity of PTSD because of functional and/or structural changes in the cardiovascular system due to repeated stress that occurs over long periods of time".

Blanchard et al (1990) proposed that PTSD might be a risk factor for hypertension. Buckley et al (2001) concluded from a meta-analysis that PTSD is associated with elevations in basal heart rate and diastolic blood pressure relative to comparison groups. They found that effect sizes for Systolic BP and Diastolic BP were statistically significant, but pressure differences were relatively small, ranging from 1 to 5 mm Hg between PTSD samples and the comparison samples. After reviewing literature he identified three hypotheses to explain why PTSD may be associated with elevated basal cardiovascular activity: First, elevations at baseline may reflect systemic changes in cardiovascular function that result from repeated cardiovascular responses to stress which is mediated by the sympathetic branch of the autonomic nervous system and may produce structural and/or functional changes in the cardiovascular system e.g. down-regulation of beta-adrenergic receptors in the heart and peripheral vasculature, which increases peripheral vascular resistance and can ultimately lead to an increase in blood pressure. Second the baseline

differences are due to either emotional priming or apprehension. This state of arousal can occur when exposure to trauma-relevant cues takes place just before physiological assessment and lowers the threshold for subsequent responding. Third hypothesis proposes that the association between PTSD and basal cardiovascular activity is mediated through variables known to have direct effects on cardiovascular health e.g. alcohol and smoking.

1. H. Predictors of the course of PTSD

Factors that have been found to be related to PTSD (in post motor vehicle accidents) at 1 year or 3 years follow-up include female sex, pretrauma Axis I co-morbidity, trauma severity, psychological reactions, and persistent health and financial problems as was concluded by research; Ehlers et al. (1998), Koren et al. (1999) and Mayou et al. (2002).

In other types of trauma such as firefighters, and domestic violence it was found that female sex, numbing experiences, comorbidity, and histories of childhood trauma are among the variables associated with chronic PTSD, Breslau and Davis, (1992); McFarlane, (1988); and Zlotnick et al., (1999).

Equivocal results was found for the effect of treatment on the course of PTSD, using data from the National Comorbidity Survey on a large, nationally representative sample of men and women, Kessler et al. (1995) found that that the length of an episode of PTSD is shorter for those who received treatment 36 months compared with those who never received treatment 64 months. In contrast, a prospective study of motor vehicle victims with PTSD reported that treatment participation was not a significant predictor of 12 month PTSD status Blanchard et al., (1996).

Bryant et al (2003-b) stressed on the importance of the role of cognitive responses as an early indicators of people who will develop PTSD. It is also possible that appraisals may help explain many of the discrepant findings about the predictive power of different symptoms. Bryant (2003-b) gave predictors for who will develop PTSD:

1. Acute stress reactions: There is a fluctuating range of symptoms post-trauma including: numbing, derealization, dissociative amnesia, intrusive thoughts, avoidance behaviors, insomnia

concentration deficits etc. These reflects the importance of the levels of distress do occur across a range of traumas within the initial month after a trauma.

2. The natural course of psychological adaptation: the typical course of adaptation is to recover in the following months after trauma exposure. In one study by Riggs et al (1995), 70% of women and 50% of men were diagnosed with PTSD at an average of 19 days after an assault; the rate of PTSD at 4 month follow-up dropped to (21%) for women and zero for men. Rothbaum et al (1992) gave similar results with rape victims, (94%) of PTSD victims within 2 weeks posttrauma, this rate dropped to (47%) at 11 weeks later.

This indicates as suggested by Bryant (2003-b) that only a minority of trauma survivors will develop long-term PTSD, and a critical task is to discriminate between those trauma survivors who will suffer transient stress reactions and those who are experiencing stress reactions that will persist into long-term disorder.

3. Acute symptoms and chronic PTSD: acute dissociation could be predictive of subsequent PTSD, re-experiencing symptoms of intrusive memories are not strong predictors of PTSD, and avoidance is not strongly predictive, hyperarousal symptoms, such as insomnia, are predictive of PTSD.

PTSD patients may display different PTSD symptoms at different times. Zoellner et al (2003), suggested that intrusive rather than avoidant dissociative models more accurately represent the encoding processes of trauma cues, and PTSD is often conceptualized as a phasic phenomenon, altering between arousal and avoidance states. Further he suggested that chronic PTSD has an avoidant− dissociative encoding style, for which they will be more amenable to a dissociative induction and to the related avoidant encoding style. Traumatized individuals with PTSD report more dissociative symptoms than those without PTSD Bremner et al., (1992).

Marshall et al (2002) indicated that PTSD develops weeks or months after the traumatic event due to a complex of psychobiological process that involves an interaction between the individual's distress and the neurohormonal response at the time of the traumatic event. The startle response in PTSD is an indication of progressive sensitization of the individual reactivity to the reminders in the environment. This concept was also supported by Miller et al (2000). Furthermore the activation of the noradrenergic system will further enhance encoding of the

emotional memories and the fear conditioning in PTSD individuals and the failure of the normal inhibitory mechanisms to suppress the stress response will also enhance the progression to PTSD Elzinga et al (2000). Another evidence foe sensitization is that childhood trauma increases the risk of adult psychopathology Heim et al 2001. Social and cultural factors were also linked to the process of sensitization Shalev (2000-a). He stated that the traumatic events are followed by "a critical period of increased brain plasticity, during which irreversible neuronal changes may occur in those who develop PTSD, he also emphasizes the importance of the environmental reactions to individuals at those times".

The role of triggers particularly sensitization for the emergence of PTSD was studied. Morgan et al (1996) have shown that the measurement of the startle response in PTSD can objectively characterize the sensitization that occurs at the fear and alarm response in PTSD. Grillon et al (1996) have highlighted that fear conditioning, kindling and sensitization contribute to the way that the repeated activation of the fear memories in PTSD, contributes to the emergence of the spontaneous intrusive memories. Bonne (2004) addressed similar issues and in particular, the question of the treatment of kindling and sensitization. The conclusion states that "an intervention aimed at improving the learned helplessness condition could curb enhanced fear conditioning, enhance escape learning and coping skills, improve a person's mood and altogether abolish the inescapable quality of the subjective experience of stress. Once this is achieved delayed averse stimuli would no longer propagate fear conditioning and lose their pervasive quality. Patients would be able to withstand and handle emotional stimuli, putting an end to the harmful process of cross sensitization and generalization, gradually expanding safe territory and limiting the effect of aversive stimuli, until the quality of life is restored".

Orr et al (2003) have highlighted that the increased heart rate in response to sudden loud tones is an acquired aspect of PTSSD. Shalev et al (2002-b) also emphasized the role of fear conditioning and novelty reactivity.

Shalev et al (2000-a) were able to demonstrate that the acquisition of an increased startle in PTSD was not related to the severity of the event or the initial intensity of the symptoms. They concluded that this was in keeping with the model of progressive neuronal sensitizations.

1. I. PTSD Remission:

Based on retrospective data from epidemiologic surveys, it has been estimated that the median time to remit from PTSD is (24.9) months Breslau et al., (1998). Furthermore Breslau (1998) found that approximately (26%) of PTSD cases remitted by 6 months, and (40%) by 12 months, from that point on, remission tapered off. The median time to remission was (24.9) months, and in more than one third of cases PTSD persisted for more than 60 months. PTSD persisted longer in women than men with median duration of (48.1) months in women vs. (12.0) months in men. PTSD persisted longer in cases resulting from traumas experienced directly, compared with learning about traumas to a loved one or a sudden unexpected death of a loved one with median duration of (48.1) months vs. (12.1) months, respectively. At least a third of subjects with PTSD never remit independent of treatment. This study by Breslau et al., (1998) gives us the following about PTSD:

(1) The lifetime prevalence of exposure to one or more traumatic events defined according to DSM-IV was (89.6%); the most prevalent trauma was sudden unexpected death of a close relative or friend (60%).

(2) Assaultive violence was higher in men, nonwhites, and persons with low socioeconomic status; other classes of trauma showed weak or no relationship with race and socioeconomic status.

(3) The conditional probability of PTSD after exposure to a representative sample of traumas experienced by the respondents was (9.2%); it was (2) fold higher in women than in men, controlling for type of trauma.

(4) Assaultive violence had the highest risk of PTSD.

(5) Sudden unexpected death of a loved one contributed a large proportion of PTSD cases (31%), because of its high rate in the population with moderate risk of PTSD.

(6) In most cases (74%), PTSD persisted for more than 6 months; the duration of PTSD was longer in women than in men and in cases resulting from trauma experienced directly than learning about trauma or sudden death of a loved one.

1. J. Risk Factors of chronic PTSD:

Brewin et al (2000) examined 77 articles in Meta analysis that included sample sizes from 1,149 to 11,000 risks PTSD in soldiers is enhanced by the effects of female gender, social economic class, education, intellectual disadvantages, and psychiatric history and to factors occurring during or after the trauma. The effects were uniform for past psychiatric history, child abuse and family psychiatric history. They also found that the following risk factors predicted PTSD more in military: female gender, younger age, race (minority status), lack of education, child hood trauma, severity of trauma, and lack of social support. The following factors were not found as differentiated predictors of PTSD between military and civilian population: low social economic status, low intelligence, other previous trauma and life stress.

The nature of the trauma is an important risk factor for developing PTSD. The severity, duration, proximity to (direct or witnessed), and type of traumatic event are the most significant risk factors for developing PTSD. Directly experienced traumatic events include the following examples: Combat, Kidnapping, Natural disasters (e.g., fire, tornado, earthquake), Catastrophic accident (e.g., auto, airplane, mining), Violent sexual assault, Violent physical assault, Witnessed traumatic events include the following examples: Seeing another person violently killed or injured, Unexpectedly seeing a dead body or body parts, Whether or not the event was perpetrated in a sadistic manner (e.g., torture, rape) occurred accidentally (e.g., fire), or occurred as an "act of God" can affect whether a person develops PTSD and whether the disorder is acute, chronic, or has a delayed onset of symptoms. Other risk factors are discussed briefly below.

Psychiatric Comorbidity is another factor that is associated with PTSD. Panic attacks may play a role in PTSD. Bryant and Panasetis (2001) suggested that (53%) to (90%) of trauma survivors during the traumatic experience have panic attacks. Furthermore they found that people with acute stress disorder are more likely to report peritraumatic and ongoing panic attacks than non-ASD individuals.

Torture is a peculiar type of trauma for the generation of PTSD that differs from other types of trauma that produce PTSD. Torture involves: deliberate abuse, perpetrators maximize fear, dread, debility in the victim, trauma is inescapable, uncontrollable, repetitive, and conditions between torture sessions undermine the recovery capacity of the victim, feelings of: guilt, shame, anger, betrayal, and humiliation; sense of security, integrity, self worth is eroded, head injury and

other physical disability. All will add to the risk of psychosocial disability, PTSD rate in this population is (38%-65%) as suggested by Roca (2002); Silove (2002).

Kucukalic et al (2002) found that PTSD is most intense and most frequent in the population of subjects who experienced the trauma of siege and war operations compared to the other group without the trauma of siege and war operations. Among war traumas torture is the most intense form of trauma leading to intensive psychopathological responses including chronic PTSD. War could be the most intense form of trauma leading to intensive psychopathological responses to a population including chronic PTSD.

As part of a larger study Koenen (2003), characterizing exposure to herbicides in Vietnam, he investigated this issue in a random sample of (1,377) American Legionnaires who had served in Southeast Asia during the Vietnam War and were followed over a (14) year period, he found that the most important risk factors included:

1. High combat exposure,
2. Perceived negative community attitudes at homecoming,
3. Minority race,
4. Depression and anger symptoms at first assessment predicted a more chronic course.

5. Community involvement at first assessment was protective and associated with decreased risk at second assessment.
6. Discomfort in disclosing Vietnam experiences was associated with an increased risk for developing PTSD but did not predict its course.
7. Combat exposure predicted PTSD course more strongly than any other risk factor.
Findings suggest recovery from PTSD is significantly influenced by perceived social support.

In this study Koenen (2003) found that at first assessment, (11.8%) of the sample met DSM-III-R criteria for PTSD. This decreased to a prevalence of (10.5%) at second assessment (1998). However, only (5.3%) of participants met criteria for PTSD at both times, (6.5%) met criteria at first assessment only, and (5.2%) met criteria at second assessment 1998 only, whereas the great majority of veterans (83.0%) did not meet criteria for PTSD at either time. Participants who met criteria at first assessment were over (14) times more likely to meet criteria at second assessment than those who did not meet criteria at first assessment.

Furthermore Koenen (2003) stressed on the importance of social support for the development of PTSD. Compared with men who never had PTSD, those with PTSD at any time were more likely to report high or medium combat exposure, report less perceived social support at homecoming, be of minority race, drink more per week at first assessment, feel more depressed at first assessment, and experience more anger at first assessment. Those with PTSD at both times reported more perceived negative community attitudes at homecoming, drank more per week, reported more depression symptoms, and expressed more anger than any other group. The first assessment group reported more community involvement as compared with the group with PTSD at both times and less help from family after returning from Vietnam, more discomfort disclosing Vietnam experiences, drinking more per week, feeling more depressed, and experiencing more anger than the second assessment (1998) group.

In the earlier study of the (1,377) Vietnam veterans Koenen (2003), (N=233, 16.9%) met criteria for PTSD for at least one time period. This was part of 14 years follow up study to study the association of PTSD over time with several potential risk factors. Significant risk factors included level of combat exposure, perceived negative community attitudes after return from Vietnam, discomfort disclosing Vietnam experiences, and depression symptoms and anger in (1984). After PTSD at first assessment, high combat exposure had a stronger association with PTSD at second assessment (1998) than did any other risk factor. Other individual risk factors that were uniquely associated with PTSD at second assessment 1998 in the final model were minority race, perceived negative community attitudes after return from Vietnam, depression symptoms, and anger at first assessment. Level of community involvement at first assessment was associated with decreased risk for PTSD at second assessment (1998) after controlling for PTSD at first assessment.

Malta et al (2002), focused on the impact of a co-occurring personality disorder on the development and remission of posttraumatic stress disorder (PTSD) in (158) motor vehicle accident (MVA) survivors followed prospectively for (1) year. Participants were assessed three times during (1991) through (1993). Prevalence of at least one personality disorder was (13.3%), with the majority (52.4%) presenting with obsessive-compulsive personality disorder. Persons with a personality disorder were significantly more likely to be diagnosed with PTSD at (1) year follow-up evaluation. For persons diagnosed with PTSD at the initial assessment, those with a personality disorder were significantly less likely to remit by (1) year. The presence of a preexisting personality disorder may increase the risk of chronic PTSD and impede remission.

Personality disorders have been identified as a negative prognostic indicator in various psychiatric disorders, and high rates of comorbidity of personality disorders and PTSD have also been reported other studies.

Cluster C personality disorders were the most prevalent, which is consistent with the reported high rates of cluster C personality disorders comorbidity with PTSD, Bollinger et al., (2000); and Southwick et al., (1993) and other anxiety disorders Brooks et al. (1991).

Hembree E et al (2004), studied (75) females with chronic PTSD as a result of rape or nonsexual assault he found that (39%) of them had a personality disorder. They found that PTSD patients with personality disorders were less likely to attain good end-state functioning, but this may be attributable to the fact that they started off slightly worse than those without personality disorders.

Chronicity could be influenced by functional impairment, comorbidity, and somatization Breslau (2001). In his study Breslau (2001) found that (82%) of PTSD will continue to do so (3) months after diagnosis, (74%) after 6 months, and median time of remission (24.9) months. The decline is up to (12) months then gentle downward slope; still (28%) had PTSD after (120) months. Factors specifically related to chronic PTSD in that study include: family history of antisocial behavior, female sex, numbing, hyperactivity to stressor, anxiety, affective disorder, coexisting medical disorders, alcohol abuse and history of childhood trauma, were also related to chronic PTSD. Somatization is another symptom related to the course of PTSD including: GI, pain, cardiopulmonary, conversion or pseudoneurologic, sexual, and female reproductive symptoms.

PTSD attracts other psychopathology like major depressive disorder, generalized anxiety disorder, substance abuse, personality disorder and other psychopathological disorders Breslau et al. (1991). They found that pure PTSD is less common than PTSD with comorbid psychiatric disorder and (83%) of PTSD sample met criteria for at least one other psychiatric disorder, compared with (44%) of those without PTSD. Moreover PTSD is not the only disorder that develops after exposure to a traumatic event. This was also supported by the National Comorbidity Survey Cramer et al (2001) who found that (88%) of men and (79%) of women with chronic PTSD met criteria for at least one other psychiatric diagnosis. In another study Kessler et al (1995) found that axis I disorders present in (85%) of male subjects with PTSD and in (80%) of female subjects. This association between PTSD and other psychiatric disorders,

particularly in the chronic type of PTSD has raised the assumption that patients with PTSD are more susceptible to other psychiatric disorders or PTSD patients may have a preexisting psychiatric disorder made them more vulnerable to PTSD. Meaghan L (2004) studied the association between PTSD and Major Depressive Disorder (MDD) in a group of (363) injury survivors just prior to discharge from hospital and 3 and 12 months post-injury. Results of this study had shed light on the prevalence of PTSD, depression, and comorbid PTSD and depression post-trauma, at (3) months 4%, 6%, and 5% respectively and (12) months 4%, 4%, and 6% respectively.

There is a strong correlation between alcoholism, substance abuse and chronic PTSD. Freeman T (2004) found no correlations between delayed PTSD symptoms and alcohol craving, although he found a significant correlations between the Obsessive Compulsive Drinking Scale OCDS and measures of lifetime alcohol and substance use. This study was done on (129) male veterans with chronic PTSD who were asked to complete the OCDS, the Mississippi Scale for combat-related PTSD symptoms, and other instruments to assess general psychopathology and lifetime alcohol and substance use.

1. K. Prognosis of Chronic PTSD:

PTSD patients are at risk for developing other mental health disorders such as panic disorder, phobias, major depressive disorder, and obsessive-compulsive disorder. Substance use and somatization were also found to be common Friedlander (2004). Furthermore Friedlander (2004) stated that the disorder significantly distresses the person and is associated with significant marital, occupational, financial, and health problems. Chronic PTSD and delayed onset PTSD is associated with psychiatric, social, and medical co-morbid states. Alcohol and substance abuse or dependence is one of the most complications in chronic PTSD. Others include: panic attacks chronic anxiety, unemployment, depression and increased risk for suicide, guilt, low self-esteem, phobias, divorce and separation. Forty percent of Vietnam veterans were estimated to have problems with drug abuse, and almost one-half of these veterans had been divorced at least once. Patients with chronic PTSD may become unemployed due to severe symptoms that interfere with their ability to execute their jobs and they cannot efficiently function in the workplace. Phobias of objects, situations, or environments that remind the person of the event often develop in these patients and it may be the cause of this problem. Panic attacks can be triggered by stimuli reminiscent of the event.

Women who were having PTSD reported more psychiatric problems, substance abuse, and lifetime exposure to domestic violence. They were significantly more likely to endorse physical health problems including obesity, smoking, irritable bowel syndrome, fibromyalgia, chronic pelvic pain, polycystic ovary disease, asthma, cervical cancer, and stroke as suggested by Dorcas et al (2004).

Suicide is one of the complications of chronic PTSD. Ninety-four patients suffering from chronic PTSD were assessed for suicidal ideation, plans and attempts in a study done by Tarrier et al (2004). In this study the prevalence of these symptoms were assessed including the characteristics of those reporting suicide-related thoughts and behavior. It was found that over half of the sample (56.4%) reported some aspect of suicidality with (38.3%) reporting suicide ideas, (8.5%) reported suicide plans and (9.6%) having made suicide attempts since the trauma. Of the nine patients who reported suicide attempts, six had made more than one attempt. The proportions of participants who reported suicidality in this sample were significantly greater than reported within the general population, when comparisons were made with an epidemiological study. Logistic regression analysis indicated that a unit increase in life impairment and depression scores were independently and significantly associated with suicidality. Multinomial regression indicated that life impairment and depression scores were associated with the presence of suicidal ideation compared to no ideation, and life impairment, depression scores and receiving psychotropic medication were associated with the presence of plans and attempts compared to no suicidal behavior. Suicide risk is elevated in those suffering from chronic PTSD and is associated with impaired functioning in combination with depression.

Friedlander (2004) found that depression, substance abuse, and physical illness are frequently accompanying PTSD. Alcohol abuse or dependence used to reduce sensations associated with hyperarousal has been especially noted among male combat veterans (52%) and female rape victims (46%). Similar rates of heavy smoking have also been noted and this likewise is a presumed method of tension reduction. In addition, it has been shown that patients with PTSD are at risk of developing physical disorders thought to be stress related such as peptic ulcer disease, asthma, hypertension, and vague chronic pain conditions whose etiology is not readily determined. PTSD is a chronic illness. In one large community survey, (53%) of patients with PTSD remained ill at 5 years, and (40%) were ill after 10 years.

Seedat et al (2003) found that psychotic phenomena may also be a relatively common manifestation in patients with chronic PTSD. Comorbid psychosis has been described in as many as (20%) to (40%) of veterans with combat-related PTSD; Hamner et al., (1999). Two studies reported rates of PTSD of 29% and 34% in mentally ill patients exposed to interpersonal violence and childhood sexual abuse, Cascardi et al. (1996); and Craine et al. (1988) respectively. Mueser et al. (1998) reported (43%) prevalence in patients with schizophrenia and bipolar disorder. Hamner et al (1999), hypothesized that severity of psychotic symptoms would also reflect severity of PTSD symptoms in patients with well-defined psychotic features which may be present in up to (40%) of patients with combat-related PTSD. In his study he found that there was a significant positive correlation between the CAPS and PANSS global ratings. Many CAPS and PANSS subscales also demonstrated significant inter correlations; however, the re experiencing and the PANSS positive symptom scale were not correlated, suggesting that psychotic features may not necessarily be influenced or accounted for by more severe re experiencing symptoms.

2. Hypotheses:

The following are the hypotheses:

1. War injured survivors with Chronic PTSD have a cluster of symptoms with severity similar to that found patients with delayed onset PTSD after 13 years of the trauma.

2. The prevalence rate of chronic PTSD is stable in the trauma survivors.

3. There are psychosocial factors that may maintain the chronicity of PTSD these include family conflicts, loss of work and early retirement, low income, divorce, the presence of axis I disorders prior to the trauma or as co morbid disorder after the trauma.

4. The rate of recovery is low due to the presence of the permanent physical disability as a source of continuous reminder of the trauma.

5. Co-morbid disorders such as depression and anxiety disorders are high with chronic PTSD and could affect the chronicity of this disorder.

6. Individuals with chronic PTSD had higher blood pressure values compared to individuals without PTSD; they may also have higher BMI due to chronic stress. There will have resting pulse rates comparable to those without PTSD. The physical parameters in PTSD such as weight and blood pressure are related to chronicity of PTSD.

3. Objectives:

The study is designed to investigate the prevalence of chronic PTSD and other psychological co-morbidities that may accompany such disorder among Kuwaiti Gulf War injured personnel. The objectives of this study based on the above hypothesis are:

1. To identify the prevalence of symptoms, cluster of PTSD symptoms and medical conditions, and psychosomatic conditions that are related to the delayed mental health state and previous exposure to traumatic events during or after Gulf War among individuals with chronic and delayed onset PTSD.

2. To identify the prevalence rate of different types of PTSD with time.

3. To identify the characteristics of chronicity in PTSD (i.e. the role of psychosocial factors) and to identify predictors of chronic PTSD.

4. To identify the role of exposures to trauma during Gulf War and their effects on PTSD recovery.

5. The rate of co-morbidities: depression, anxiety and other psychological morbid disorders among war physically injured victims with and without PTSD.

6. To identify the prevalence and association between physical parameters: resting pulse rate, blood pressure, BMI and chronic PTSD.

4. Results:

4. A. PTSD classification:

4. A. 1. PTSD in the 1st and 2nd assessments:

Comparing the PTSD results of the first and second assessment (123 participants who were assessed in the two phases of the study) we can separate participants to the following four groups:

1. Delayed onset PTSD (N=18, 14.6%): are those who have PTSD in the second assessment and no assessment at the 1st assessment in 1998.

2. Chronic PTSD (N=19, 15.4%): those participants who continued to have PTSD throughout the 1st and 2nd assessments.

3. Participants who recovered from PTSD after the 1st assessment in (1998), (N=28, 22.8%).

4. There were N=58 (47.2%) of the participants who did not have PTSD at both assessments.

4. A. 2. PTSD in the 2nd assessment with 33 cases (injured):

As it was explained in the methods section only 123 of the participants in the 1st phase of the study had participated in the second phase. New members had joined the injured sample that had the same characteristics: i.e. all of the new 33 participants are war injured due the Gulf War in 1990-1991. The following was found about the PTSD for the whole sample of 156 participants (N=47, 30.1%) had PTSD (chronic and delayed onset) and (N=109, 69.9%) had no PTSD (never or recovered PTSD).

The analysis below was based on the above classification: either the four groups: Chronic (N=19), never (N=58), delayed (N=18) and recovered (N=28) PTSD. Another analysis was based on dividing the sample into PTSD group (N=47) and no-PTSD group (N=109).

4. B. Socio-demographic Characteristics:

With several independent tests, the nominal (p) value of .05 is inflated, so I used the Bonferroni correction procedure in each case. For the demographic data there were 8 variables, so the corrected p value was .006. Any test with a p value less than .06 is significant at the 5% level. The variables included are: age, gender, social status, education, employment, income, life standard and past psychiatric history.

4. B. 1. Age

The mean age of PTSD group is (40.17 years) and for the no-PTSD group is (42.5 years) (F=2.2, p=.136). The chronic PTSD group has the lowest mean age (38.1 years) but it was not significant comparing it with other subtypes of PTSD as shown in Table 1.

Table.1. Mean age and Sub-types of PTSD in 2003

PTSD	Mean	N	SD
Never PTSD	42.95	58	8.998
Lifetime PTSD	43.96	28	9.442
Delayed PTSD	40.17	18	9.948
Chronic PTSD	38.11	19	6.350
Total	42.02	123	9.026

4. B. 2. Gender:

There were five females in the sample, one had chronic PTSD and another had delayed onset PTSD Table2. The females in this study are 3.2% of the sample; hence analysis based on gender was not made.

Table. 2. PTSD subtypes and gender

			Gender		Total
			Male	Female	
PTSD	Never PTSD	N	57	1	58
		%	98.3%	1.7%	100.0%
	Lifetime PTSD	N	26	2	28
		%	92.9%	7.1%	100.0%
	Delayed PTSD	N	17	1	18
		%	94.4%	5.6%	100.0%
	Chronic PTSD	N	18	1	19
		%	94.7%	5.3%	100.0%
Total		N	118	5	123
		%	95.9%	4.1%	100.0%

4. B. 3. Social Status

For those with PTSD (8.5%) were bachelors and (91.5%) were married and those without PTSD (4.6%) and (95.4%) respectively without statistically significant difference (p=.269). There were no significant difference comparing subtypes of PTSD and social status Table 3. PTSD participants rated their marriage as 27.9% excellent and 20.9% as bad vs. 45.2% and 9.6% for non-PTSD participants respectively. This was not statistically significant P=0.137 Table 4.

Table. 3. Social status of participants and PTSD subtypes.

		PTSD				Total	df	Sig.
		Never	Lifetime	Delayed	Chronic			
Bachelor	N	3	2	3	1	9	3	.418
Divorced	%	5.2%	7.1%	16.7%	5.3%	7.3%		
Married	N	55	26	15	18	114		
	%	94.8%	92.9%	83.3%	94.7%	92.7%		
Total	N	58	28	18	19	123		
	%	100%	100%	100%	100%	100%		

Table. 4. Rating satisfaction in social life and subtypes of PTSD

		PTSD				Total	df	Sig.
		Never	Lifetime	Delayed	Chronic			
Excellent	N	23	14	5	5	47	9	.442
	%	43.4%	50.0%	33.3%	27.8%	41.2%		
Very good	N	12	4	3	6	25		
	%	22.6%	14.3%	20.0%	33.3%	21.9%		
Good	N	15	5	4	6	30		
	%	28.3%	17.9%	26.7%	33.3%	26.3%		
Bad	N	3	5	3	1	12		
	%	5.7%	17.9%	20.0%	5.6%	10.5%		
Total	N	53	28	15	18	114		
	%	100%	100%	100%	100%	100%		

4. B. 4. Education

There were no statistically significant differences between PTSD and non-PTSD group in level of education P= 0.895, moreover here were no significant differences between PTSD subgroups and education level Tale 5.

Table. 5. PTSD subtypes and education level

		PTSD				Total	df	Sig.
		NO	Lifetime	Delayed	Chronic			
Not Read or	N	2	1	1	1	5	21	.991
Write	%	3.4%	3.6%	5.6%	5.3%	4.1%		
Read and	N	3	0	0	1	4		
Write	%	5.2%	.0%	.0%	5.3%	3.3%		
Elementary	N	2	1	0	1	4		
	%	3.4%	3.6%	.0%	5.3%	3.3%		
Intermediate	N	15	9	4	7	35		
	%	25.9%	32.1%	22.2%	36.8%	28.5%		
Secondary	N	11	5	4	1	21		
	%	19.0%	17.9%	22.2%	5.3%	17.1%		
Diploma	N	14	8	5	5	32		
	%	24.1%	28.6%	27.8%	26.3%	26.0%		
University	N	9	4	3	3	19		
	%	15.5%	14.3%	16.7%	15.8%	15.4%		
Master	N	2	0	1	0	3		
	%	3.4%	.0%	5.6%	.0%	2.4%		
Total	M	58	28	18	19	123		
	%	100.0%	100.0%	100.0%	100.0%	100.0%		

4. B. 5. Employment:

Employment was not different between the two groups PTSD vs. non-PTSD employed 80.4%, 84.1% respectively P=0.367. There was no statistically significant difference between PTSD subtypes and employment status Table 6.

Table. 6. Employment and PTSD subtypes

		PTSD				Total	df	Sig.
		NO	Lifetime	Delayed	Chronic			
YES	N	46	27	15	14	102	3	.235
	%	80.7%	96.4%	83.3%	77.8%	84.3%		
NO	N	11	1	3	4	19		
	%	19.3%	3.6%	16.7%	22.2%	15.7%		
Total	N	57	28	18	18	121		
	%	100%	100%	100%	100%	100%		

4. B. 6. Income and family members

There were no significant differences between PTSD subtypes and monthly income as shown in Table 7. The mean family size for PTSD subtypes was for: never PTSD ($\overline{X}$ =7.1), lifetime PTSD ($\overline{X}$ =8), delayed onset PTSD ($\overline{X}$ =8.2) and chronic PTSD ($\overline{X}$ =7) with (F=.540, p=.656).

Table. 7. Monthly Income (Kuwaiti Dinar KD: 3.3 US$ for 1 KD) and PTSD

Income Kuwait Dinar (KD) (3.3 US$ for 1 KD)	PTSD				Total
	Never	Lifetime	Delayed	Chronic	
<600	9	2	6	8	25
	15.5%	7.1%	33.3%	41.1%	20.3%
601-1000	32	17	10	7	66
	55.2%	60.7%	55.6%	36.8%	53.7%
1000-2000	16	7	2	4	29
	27.5%	24.3%	11.2%	21.1%	23.5%
>2000	1	2	0	0	3
	1.7%	7.2%			2.4%
Total	58	28	18	19	123
	100%	100%	100%	100%	100%

Chi –Square: df=9, p=.078

4. B. 7. Change in life standard after the trauma

Participants with delayed onset PTSD showed significant changes in life standard after the trauma (p=.037) compared to other PTSD subtypes Table 8. PTSD participants had significant changes in living standards after the trauma (p=.031) compared to participants without PTSD Table 9.

The following factors showed significant differences: activities were restricted due to psychiatric problems (p<.001), activities not done due to psychiatric problems (p<.001), feeling less calm and peaceful (p<.001), low energy (p=0.026), feeling depressed (p<0.001), feeling sad (p<.001), distressed (p<.001), interfered with social activities (p<.001), frequent temper changes (p=0.004), nervousness (p=0.009), anxious (p<0.001), irritability (p< 0.001), loneliness (p<.001), tired without clear cause (p=0.002).

Table. 8. PTSD subtypes and Change in living standard due to the trauma

	Change in living standard due to the trauma			Total
	No change	Worse	Much Worse	
Never PTSD	42	15	1	58
	72.4%	25.9%	1.7%	100%
Lifetime PTSD	13	13	2	28
	46.4%	46.4%	7.1%	100%
Delayed onset PTSD	4	11	3	18
	22.2%	61.1%	16.7%	100%
Chronic PTSD	10	8	1	19
	52.6%	42.1%	5.3%	100%
Total	69	47	7	123
	46.1%	38.2%	5.7%	100%

Chi-Square: Sig. =.037, df=12

Table. 9. PTSD and Change in living standard due to the trauma

Change in living standard	PTSD		Total
	NO PTSD	PTSD	
No change	73	20	93
	67%	46.5%	59.7%
Worse	33	23	56
	30.3%	48.9%	35.9%
Much Worse	3	4	7
	2.8%	8.5%	4.5%
Total	109	47	156
	100.0%	100.0%	100.0%

P=.013

4. B. 8. Past Psychiatric History

Past psychiatric history was significantly different between PTSD (76.1%) and non-PTSD (38.5%) participants P<0.0001. There was a significant difference p<.001 between different PTSD subtypes and past psychiatric history, participants with chronic PTSD (N=18, 94.7%) and participants with delayed onset PTSD (N= 12, 70%) Table 10.

Table. 10. Past Psychiatric History and PTSD subtypes

	PTSD				Total
	NO	Lifetime	Delayed	Chronic	
No Past Psychiatric	39	14	5	1	59
Problems	70.9%	51.9%	29.4%	5.3%	50.0%
Past Psychiatric	16	13	12	18	59
Problems	29.1%	48.1%	70.6%	94.7%	50.0%
Total	55	27	17	19	118
	100.0%	100.0%	100.0%	100.0%	100.0%

Chi-Square: df=3, p<.001

4. C. PTSD:

4. C. 1. Trauma

Although all the participants were war-injured survivors and the questions in CAPS were directed as war the traumatic event, only (85.1%) of participants with PTSD and (72.5%) of participants without PTSD scored war as the most stressful event they have experienced up to the assessment for this study. Non war traumas included death of a relative, accidents, loses etc. of PTSD participants had more prevalence of being a victim of crime prior to the trauma (29.8%) compared to no-PTSD participants (11.9%) (p=.008) Table 11. War as the most stressful event was also found to be more prevalent in participants with chronic PTSD, and being a victim of a crime was more prevalent in delayed onset and chronic PTSD (Table 12).

Table. 11. Trauma and PTSD

	PTSD		No-PTSD		p
	N	%	N	%	
War trauma most stressful event	40	85.1	79	72.5	.064
Severe accident	21	44.7	50	45.9	.516
Victim of a crime*	14	29.8	13	11.9	.008
War most stressful for family	37	78.7	80	73.4	.311

*p<.05

Table. 12. Trauma and PTSD subtypes

Type of trauma	Never PTSD		Lifetime PTSD		Delayed PTSD		Chronic PTSD	
	N	%	N	%	N	%	N	%
War trauma most stressful event	39	67.2	23	82.1	14	77.8	19	100
Severe accident	27	46.6	12	42.9	9	50	8	42.1
Victim of a crime	6	10.3	4	14.3	6	33.3	6	31.6
War most stressful for family	39	67.2	21	75	13	72.2	16	84.2

4. C. 2. PTSD - CAPS

The prevalence of PTSD 30%: delayed onset PTSD (N=18, 14.6%) and chronic PTSD (N=19, 15.4%).

4. C. 3. Severity of PTSD symptoms

4. C. 3. A. Total PTSD symptoms - CAPS:

Participants with chronic PTSD had the highest mean PTSD score using CAPS ($\overline{X}$ =71), and those with delayed onset PTSD ($\overline{X}$ =64.6) but without statistical significant difference (p=.993) Table 13.

There were no differences between participants with Chronic and delayed onset PTSD in mean total intrusive and arousal symptoms, but they were having higher ($\overline{X}$ =27.3) of avoidance symptoms compared to delayed onset PTSD ($\overline{X}$ =23.7) but it was statistically not significant (p=.152) Table 14.

Table. 13. Severity of PTSD symptoms using CAPS

PTSD	Mean	N	SD	df	F	Sig
Never PTSD	15.95	58	14.633	3	80.44	0.0001
Lifetime PTSD	26.14	28	15.005			
Delayed PTSD	64.67	18	19.385			
Chronic PTSD	71.00	19	19.253			
Total	33.90	123	27.892			

Chi-Square: (Chronic and delayed onset PTSD) F=.000, p=.993

Table. 14. PTSD symptoms in PTSD subtypes.

PTSD		Intrusion	Avoidance	Arousal
Never PTSD	Mean	2.8793	6.6379	6.4310
	SD	4.40127	8.58129	6.85466
Lifetime PTSD	Mean	7.1786	8.5714	10.3929
	SD	6.92849	8.22115	6.86558
Delayed PTSD	Mean	18.2778	23.7222	22.6667
	SD	9.11886	7.55221	7.27607
Chronic PTSD	Mean	18.2632	27.3684	25.3684
	SD	8.14345	7.57342	7.45513

Chi-Square: Intrusion F=.000, p=.996. Avoidance F=2.148 p=.152. Arousal F=1.24 p=.273

4. C. 3. B. PTSD symptoms in 1998 (1st assessment) and 2003 (2nd assessment):

Table 15 shows that participants with PTSD with higher mean symptoms of intrusions, avoidance and arousal in (1998) 1st phase of the study are those who subsequently in (2003) 2nd phase who developed chronic PTSD. Participants with mild PTSD symptoms in the 1st phase with lower means of PTSD symptoms are those who recovered from PTSD in the second assessment and were diagnose as lifetime PTSD. The participants without PTSD diagnosis in 1st phase with high and low mean symptoms respectively are those who subsequently developed late onset PTSD and who never developed PTSD respectively Table 16.

Table. 15. PTSD in 1998 and PTSD subtypes in 2003 2nd phase using CAPS mean scores

1998 (1st phase)				
	Severe PTSD	NO PTSD diagnosis With PTSD Symptoms	Mild PTSD	NO PTSD without PTSD symptoms
Intrusion	20.7	5.3	17.6	3.2
Avoidance	33.3	8.4	26.4	4.4
Arousal	30.4	9.5	22.4	5.1
Total PTSD	84.4	23.2	66.5	12.6
2003 (2nd phase)				
PTSD Diagnosis	Chronic	Delayed	lifetime	Never
Intrusion	15.0	14.5	5.5	2.4
Avoidance	27.3	23.7	8.6	6.6
Arousal	28.5	26.3	12.0	6.8
Total PTSD	71.0	64.6	26.1	15.9

Table. 16. PTSD diagnosis in 2003 and total score of PTSD symptoms 1998 One way ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	8616.583	3	2872.194	3.060	.031
Within Groups	111678.458	119	938.474		
Total	120295.041	122			

4. C. 4. Predictors of PTSD

In our sample it was found that intrusion, avoidance, arousal, total PTSD symptoms in 1st assessment in (1998) was significantly predicting the severity and the development of PTSD in the 2nd assessment in (2003) Table 17. The same findings were found for PTSD associated symptoms in 1st assessment as predictors of severity and PTSD diagnosis in the 2nd assessment in (2003) Table 18. With several independent tests for the following 8 predictors of PTSD, the nominal (p) value of .05 is inflated, so I used the Bonferroni correction procedure in each case. For the predictors of PTSD there were 8 variables, so the corrected p value was .006. Any test with a p value less than .06 is significant at the 5% level. The following variables: guilt not taking an action, survivor's guilt, homicide, disappointed with others, hopelessness, memory, depressed, overwhelmed.

Table. 17. Correlations PTSD symptoms in 1st assessment in 1998 as predictors of total PTSD symptoms and PTSD diagnosis in 2nd assessment in 2003

First Assessment 1998	TOTAL PTSD Symptoms 2003	PTSD Diagnosis 2003
Intrusions	0.37**	0.26**
Avoidance	0.40**	0.31**
Arousal	0.45**	0.34**
Total PTSD	0.44**	0.33**
PTSD Diagnosis	0.29**	0.17 (P=.06)

**p<.001

Table. 18. Correlations PTSD associated symptoms in 1st assessment in 1998 as predictors of total PTSD symptoms and PTSD diagnosis in 2nd assessment in 2003

First Assessment 1998	TOTAL PTSD Symptoms 2003	PTSD Diagnosis 2003
Guilt Not taking an Action	0.17	0.17
Survivors Guilt	0.31**	0.24*
Homicide	0.14	0.07
Disappointed with others	0.22*	0.26**
Hopelessness	0.25*	0.25*
Memory	0.20*	0.21*
Depressed	0.33**	0.27**
Overwhelmed	0.39**	0.32**
Total Associated Symptoms	0.38**	0.35**

* p<.05 ** p<.001

4. C. 5. PTSD associated symptoms

PTSD associated symptoms included in CAPS includes: guilt not taking an action, survivors guilt, homicide, disappointed with others, hopelessness, memory problems, depressed and overwhelmed. Participants with chronic PTSD were found to have higher mean of total PTSD associated symptoms compared to other PTSD subtypes Table 19.

Table. 19. PTSD associated symptoms in 1st assessment 1998 and 2nd assessment 2003

PTSD	Mean total score of associated symptoms of PTSD 1st assessment	Mean total score of associated symptoms of PTSD 2nd assessment
Never PTSD	5.89	6.77
Lifetime PTSD	22.92	8.57
Delayed PTSD	12.00	12.00
Chronic PTSD	32.0	18.05

4. C. 6. Treatment

There were no statistical significant difference between PTSD subtypes and the use of psychiatric medications for different causes (p=.205).

4. D. PTSD and Injury:

All the participants were war injured survivors that had sustained different kind and degree of physical injury. Table 20 shows distribution of the sample according to the injuries of different parts of the body. In our sample the mean injury score was ($\overline{X}$ =138.1), the maximum injury score was (460) and the minimum injury score was (10). The injury scores were assigned according to Kuwait law for compensation of injury disability (see appendices section).

There were no significant differences between subtypes of PTSD and mean of total injury score Table 21.

Table. 20. Types of injury, Injury score.

	Torture	Head	Eye	Tongue	Teeth Jaw	Nose	Ear	Neck
N (%)	70 (56.9)	7(5.6)	5(4)	1(0.8)	5(4)	3(2.4)	7(5.6)	15(12)
Mean	42.8	19.4	25.6	33.0	20.0	32.6	93.5	31.0
Minimum	5.0	5.0	5.0	33.0	5.0	25.0	25.0	5.0
Maximum	230.0	50.0	55.0	33.0	45.0	40.0	150.	100.

Table. 20. Types of injury, Injury score. … Continue

	Spine	Chest	Abdomen	Upper Extremities	Lower Extremities	Genitalia
N (%)	26(21.1)	22(17.8)	21(17)	40(32.5)	46(37.3)	4(3.2)
Mean	39.8	17.7	30.0	64.0	51.6	103.7
Minimum	5.0	5.0	5.0	5.0	5.0	50.0
Maximum	300.0	60.0	100.0	295.0	270.0	140.0

Table. 21. Total Injury Score Due To All Injuries

	Mean	SD	95% Confidence Interval for Mean		df	F	P
			Lower Bound	Upper Bound			
1 Never PTSD	150.74	124.02	112.09	189.38	3	0.67	0.57
2 Recovered PTSD	108.05	85.98	67.81	148.29			
3 Delayed PTSD	150.29	146.95	65.44	235.13			
4 Chronic PTSD	129.73	94.83	66.02	193.43			

(Chronic and never PTSD F=1.911, p=.173)

4. E. Co morbid psychiatric disorders:

The following co morbid psychiatric disorders were independent variables: generalized anxiety disorder GAD, major depressive disorder MDD, dysthymia, OCD, panic, psychoticism, somatization and hostility. With these several independent tests 8 co morbid disorders with PTSD, the nominal (p) value of .05 is inflated, so I used the Bonferroni correction procedure in each case. The corrected p value was .006. Any test with a p value less than .06 is significant at the 5% level.

4. E. 1. Generalized Anxiety Disorder (GAD)

Five (3.2%) of our participants had GAD based on ICD-10 using CIDI (3) had chronic PTSD and (2) had delayed onset PTSD. Tables 22 shows that Anxiety symptoms were more prevalent among participants with chronic PTSD compared to other PTSD subtypes ($p<.001$) with significant higher mean score of anxiety ($p<.001$).

Table. 22. Distribution of: SCL-90R scores, and CIDI diagnosis by PTSD subtypes

	Never PTSD	Lifetime PTSD	Delayed PTSD	Chronic PTSD	p
Anxiety SCL-90 (1.76-4)	5 (8.6%)	5 (17.9%)	5 (27.8%)	11 (57.9%)	**
GAD ICD-10 CIDI	0	0	2 (11.1%)	3 (15.8%)	**
MDD ICD-10 CIDI	0	0	4 (22.2%)	2 (10.5%)	**
Depression SCL-90R (1.76-4)	7 (12.1%)	3 (10.7%)	10 (55.6%)	12 (63.2%)	**
Dysthymia	0	0	1 (5.6%)	0	-
OCD SCL-90R	1 (1.7%)	1 (3.6%)	2 (11.1%)	8 (42.1%)	**
OCD ICD-10 CIDI	0	0	0	2 (10.5%)	*
Panic ICD-10 CIDI	0	1(3.6%)	1 (5.6%)	4 (21.1%)	**
Psychoticism	4(6.9%)	3 (10.7%)	1 (5.6%)	8 (42.1%)	**
Somatization	2 (3.4%)	1 (3.6%)	4 (22.2%)	7 (36.8%)	**
Hostility	1 (1.7%)	2 (7.1%)	1 (5.6%)	7 (36.8%)	**

*p<.05 **p<.001

4. E. 2. Panic Disorder

In our sample (N=9, 5.8%) of the participants had panic disorder based on ICD-10 criteria using CIDI: (4) had chronic PTSD, (2) had delayed onset PTSD and (3) they have never had PTSD.

4. E. 3. Obsessive Compulsive Disorder (OCD)

There was four (2.6%) of the participants that had criteria of OCD based on ICD-10 using CIDI: (2) of these participants had chronic PTSD, (1) had delayed onset PTSD (new group) and (1) never had PTSD. The participants with chronic PTSD had significant higher prevalence of OCD compared to other PTSD subgroups Table 22.

4. E. 4. Somatization:

Somatization was significantly more prevalent in participants with chronic PTSD Tables 22. Moderate to severe symptoms of hostility and moderate to severe symptoms of psychoticism were found more in chronic PTSD individuals.

4. E. 5. Depression:

4. E. 5. A. Major Depressive Disorder (MDD)

Based on ICD-10 (CIDI) (N=9, 5.8%) had criteria of major depressive disorder (MDD). Five of the participants had delayed onset PTSD (one from the new group), (2) with chronic PTSD and 2 had no PTSD. Those with PTSD (chronic and delayed onset) (37) participants (59.4%) had depression. Participants without PTSD (recovered and those who never had PTSD) (86), (11.6%) had depression Table 22.

4. E. 5. B. Dysthymia

There were two participants that had Dysthymia (1.3%) of the participants this diagnosis was based on ICD-10 criteria using CIDI both of them had delayed onset PTSD (one of them from the new group).

4. F. Physical parameters in PTSD

The following physical parameters: blood pressure, pulse pressure, resting pulse rate, Body Mass Index (BMI) and Waste-Hip Ratio (WHR) were 5 independent variables that were measured in this study. With these several independent tests, the nominal (p) value of .05 is inflated, so I used the Bonferroni correction procedure in each case. For the physical parameters with PTSD there were 5 variables, so the corrected p value was .010. Any test with a p value less than .01 is significant at the 5% level

4. F. 1. Blood Pressure (BP):

The mean systolic BP of the sample ($\overline{X}$ =135.4 mmHg), and the diastolic BP ($\overline{X}$ =86.5). In our sample (N=24, 15.4%) had systolic hypertension Table 23. There were no significant differences between BP measure during the interview and participants with or without PTSD subtypes Table 24.

The mean systolic and diastolic BP were higher among participants with chronic PTSD ($\overline{X}$ =140.8 mmHg and $\overline{X}$ =88.8 mmHg respectively). There was statistically significant difference (p=.008) in the systolic BP between participants with chronic PTSD and those with delayed onset PTSD Table 25. Individuals with chronic PTSD have the lowest pulse pressure compared to life time and delayed onset PTSD but it was statistically not significant Table 26.

Table. 23. Blood Pressure

	Frequency	Percent
1. Normal	30	19.2
2. Pre hypertension	47	30.1
3. Stage:1 Hypertension	33	21.2
4. Stage:2 Hypertension	22	14.1
5. Systolic Hypertension	24	15.4
Total	156	100.0

Table. 24. PTSD subtypes and 1998 AND PTSD 2003

	Blood Pressure BP					Total
	Normal	Pre Hypertension	Stage:1 Hypertension	Stage:2 Hypertension	Systolic Hypertension	
Never PTSD	9	22	14	6	7	58
	15.5%	37.9%	24.1%	10.3%	12.1%	100%
Lifetime PTSD	6	9	3	5	5	28
	21.4%	32.1%	10.7%	17.9%	17.9%	100%
Delayed PTSD	4	3	3	5	3	18
	22.2%	16.7%	16.7%	27.8%	16.7%	100%
Chronic PTSD	4	6	3	2	4	19
	21.1%	31.6%	15.8%	10.5%	21.1%	100%

Chi-Square df=12 (p=.726)

Table. 25. Systolic and Diastolic BP and PTSD subtypes

PTSD		Systolic BP	Diastolic BP
Never PTSD	Mean	135.2759	85.9828
	N	58	58
	SD	16.04248	10.19544
Lifetime PTSD	Mean	135.6786	86.8214
	N	28	28
	SD	17.49297	12.69311
Delayed PTSD	Mean	140.8333	88.8333
	N	18	18
	SD	23.59025	14.60560
Chronic PTSD	Mean	130.5263	84.9474
	N	19	19
	SD	11.79156	10.10761

Systolic BP T-test: Chronic and delayed onset PTSD: F= 7.95, df=35 p=.008.

Table. 26. Pulse pressure and PTSD subtypes

PTSD	Mean	Std. Deviation
Never PTSD	49.34	11.016
Lifetime PTSD	47.64	8.450
Delayed PTSD	47.80	12.751
Chronic PTSD	45.39	10.256
Total	48.14	10.592

F0.662, df=3, p=0.577

4. F. 2. Pulse Rate (PR):

The mean resting pulse rate for the sample was ($\overline{X}$ =76/minute). There were no significant differences in pulse rate between participants with and those without PTSD Table 27.

Table. 27. One-way analysis of variance (ANOVA) for Pulse and PTSD subtypes

	N	Mean	SD	95% Confidence Interval for Mean		Minimum	Maximum
				Lower Bound	Upper Bound		
1 Never PTSD	58	77.98	9.738	75.42	80.54	56	101
2 Lifetime PTSD	28	76.61	9.616	72.88	80.34	61	96
3 Delayed PTSD	18	74.44	8.913	70.01	78.88	55	96
4 Chronic PTSD	19	76.58	9.617	71.94	81.21	63	97
Total	123	76.93	9.537	75.23	78.64	55	101

ONEWAY ANOVA: PR F=.657, p=.58

4. F. 3. Body Mass Index (BMI):

The mean BMI for the sample was ($\overline{X}$ =30.18). The sample was classified based on BMI as shown in Table 28 to: normal weight, pre-obese, obese I, II and III. There was no statistical significance between PTSD subtypes and BMI Table 29.

Table. 28. Body Mass Index

	N	%
NORMAL WEIGHT (18~24.9)	45	28.8
PRE-OBESE(25~29.9)	58	37.2
OBESE-I(30~34.9)	31	19.9
OBESE-II(35~40)	11	7.1
IBESE-III(> 4O)	11	7.1

Table. 29. One-way analysis of variance (ANOVA) for BMI and PTSD subtypes

	N	Mean	SD	95% Confidence Interval for Mean		Minimum	Maximum
				Lower Bound	Upper Bound		
Never PTSD	58	30.8296	21.50718	25.1746	36.4846	16.53	184.89
Lifetime PTSD	28	29.2110	6.49125	26.6940	31.7281	20.81	43.42
Delayed PTSD	18	29.7163	7.65410	25.9100	33.5226	19.83	43.27
Chronic PTSD	19	28.6280	6.18933	25.6449	31.6112	19.35	40.90
Total	123	29.9582	15.49283	27.1928	32.7235	16.53	184.89

ONEWAY ANOVA: BMI F=.128, p=.943

4. F. 4. Waste-Hip Ratio (WHR):

The mean WHR for the sample was ($\overline{X}$ =0.946). In our sample we found that (N= 128, 82.1%) had risk due to high WHR ratio. There was no statistical significant difference between PTSD subtypes and WHR Table 30.

Table. 30. WHR and PTSD subtypes

PTSD	Mean	N	SD
Never PTSD	.9418	58	.04594
Lifetime PTSD	.9508	28	.04959
Delayed PTSD	.9485	18	.11323
Chronic PTSD	.9500	19	.06007

Chi-Square: F=.177 p=.912

4. G. Life Events:

The mean sore of LES of the sample was ($\overline{X}$ =264.5). In our sample (N=56, 35.9%) of the sample scored (>300). The mean score of participants with PTSD ($\overline{X}$ =361.6) and participants with no-PTSD ($\overline{X}$ =222.7) with (p<.001). Participants with chronic PTSD had significantly high mean score of LES ($\overline{X}$ =397.2) Table 31.

Table. 31. Total of LES and PTSD subtypes

PTSD	Mean	N	SD
Never PTSD	196.810	58	137.99268
Lifetime PTSD	284.535	28	165.83269
Delayed PTSD	362.888	18	162.31773
Chronic PTSD	397.210	19	236.35745

F=9.4, df=3 p=.001

4. H. Personality

Eysenck personality questionnaire (EPQ) was used in this study three dimensions discussed: psychoticism, neuroticism and extraversion. Table 32 showing bivariate correlations between PTSD cluster symptoms: Intrusions, avoidance and arousal and EPQ dimensions. It was found that both neuroticism and psychoticism were correlated significantly with PTSD cluster symptoms (p<0.001) but not extraversion. The 3 independent variables that were included in the analysis: psychoticism, neuroticism and extraversion were the nominal (p) value of .05 is inflated, so I used the Bonferroni correction procedure in each case. The corrected p value was .016. Any test with a p value less than .01 is significant at the 5% level

4. H. 1. Psychoticism

In our sample (N=7, 4.5%) had moderate psychoticism symptoms using EPQ. Participants with chronic PTSD had the highest mean of psychoticism ($\overline{X}$ =6.2) with statistical significance (p=.001) Table 33.

4. H. 2. Neuroticism

Severe neuroticism was found in (N=55, 35.5%) and moderate neuroticism in (N=61, 39.1%). The highest mean value of neuroticism was observed in participants with chronic PTSD ($\overline{X}$ =18.37) with (p<.001).

4. H. 3. Extraversion

Severe extraversion symptoms using EPQ was observed in (N=48, 30.8%) and moderate extraversion in (N=88, 56.4%). Extraversion was seen with higher mean values in participants who never had PTSD or those who recovered from PTSD ($\overline{X}$ =13.12 and $\overline{X}$ =13.14 respectively) with (p=.026).

Table. 32. Bivariate correlation using EPQ: and PTSD cluster symptoms.

		EPQ : Psychoticism SCALE	EPQ : Neuroticism SCALE	EPQ : Extroversion SCALE	Arousal	Avoidance	Intrusion
EPQ : Psychoticism SCALE	Pearson Correlation		.356(**)	-.159	.323(**)	.316(**)	.325(**)
	Sig. (2-tailed)		.000	.061	.000	.000	.000
	N		139	139	139	139	139
EPQ : Neuroticism SCALE	Pearson Correlation			-.270(**)	.666(**)	.543(**)	.402(**)
	Sig. (2-tailed)			.001	.000	.000	.000
	N			139	139	139	139
EPQ : Extroversion SCALE	Pearson Correlation				-.307(**)	-.359(**)	-.278(**)
	Sig. (2-tailed)				.000	.000	.001
	N				139	139	139
Arousal	Pearson Correlation					.693(**)	.670(**)
	Sig. (2-tailed)					.000	.000
	N					139	139
Avoidance	Pearson Correlation						.678(**)
	Sig. (2-tailed)						.000
	N						139
Intrusion	Pearson Correlation						
	Sig. (2-tailed)						
	N						

** Correlation is significant at the 0.01 level (2-tailed).

Table 33. EPQ: Psychoticism, Neuroticism, and Extraversion and PTSD subtypes.

PTSD		Psychoticism	Neuroticism	Extroversion
Never PTSD	Mean	3.43	10.64	13.12
	N	58	58	58
	SD	2.112	4.752	3.038
Lifetime PTSD	Mean	4.32	13.32	13.14
	N	28	28	28
	SD	2.495	4.514	3.798
Delayed PTSD	Mean	4.61	15.00	11.61
	N	18	18	18
	SD	2.429	4.728	4.340
Chronic PTSD	Mean	6.21	18.37	10.42
	N	19	19	19
	SD	3.809	3.337	4.562

Psychoticism ($F=5.79$, $df=3, 119$, $p=.001$) Neuroticism ($F=15.5$, $df=3,119$, $p<.001$) Extraversion ($F=3.2$, $df=3,119$, $p=.026$)

4. I. Summary of the results

4. I. 1. PTSD and different physical parameters:

Tables 34 to 36 summarize PTSD and no-PTSD participants and different variable tested in this study. Bonferroni correction was used for the different physical and psychological parameters data there were 22 variables, so the corrected p value was .0023. Any test with a p value less than .02 is significant at the 5% level

Table 34. PTSD and different physical and psychological parameters

Variables	NO PTSD N=86		PTSD N=37		t	p ≤
	Mean	SD	Mean	SD		
Age	43.28	9.10	39.11	8.25	2.396	0.0181*
BMI	30.30	18.00	29.16	6.86	0.375	0.7086
BP	2.70	1.29	2.89	1.45	-0.736	0.4629
PR	77.53	9.66	75.54	9.22	1.064	0.2894
EPQ-P	3.72	2.27	5.43	3.27	-3.339	0.0011**
EPQ-N	11.51	4.82	16.73	4.36	-5.662	0.0001**
EPQ-E	13.13	3.28	11.00	4.43	2.955	0.0038*
SOM	0.60	0.63	1.38	0.98	-5.256	0.0001**
OC	0.62	0.62	1.43	1.00	-5.457	0.0001**
IS	0.46	0.59	1.29	1.11	-5.446	0.0001**
DEP	0.57	0.57	1.47	1.04	-6.132	0.0001**
ANX	0.35	0.57	1.16	1.14	-5.274	0.0001**
HOS	0.36	0.55	1.22	1.19	-5.466	0.0001**
PHOB	0.24	0.46	0.94	1.05	-5.206	0.0001**
PAR	0.68	0.66	1.39	1.14	-4.339	0.0001**
PSY	0.31	0.44	0.88	0.86	-4.859	0.0001**
GSI	0.48	0.49	1.27	0.96	-6.010	0.0001**
PST	22.51	20.60	49.16	27.86	-5.893	0.0001**
PSDI	1.92	0.49	2.19	0.66	-2.494	0.0140*
SCL-DEP	1.39	0.38	2.03	0.71	-6.537	0.0001**
SCL-ANX	1.24	0.37	1.81	0.80	-5.429	0.0001**
SCL-TOT	1.33	0.36	1.94	0.73	-6.227	0.0001**

* $p \leq .05$

** $p \leq .001$

4. I. 2. PTSD Subtypes

Table. 35. PTSD subtypes and psychosocial variables

	Never PTSD	Lifetime PTSD	Delayed PTSD	Chronic PTSD	p
Age	42.9±8.9	43.9±9.4	40.1±9.9	38.1±6.3	.099
Married	98.4%	92.9%	83.3%	94.7%	.418
Not satisfied socially	5.7%	17.9%	20%	5.6%	.442
Not working	19.3%	3.6%	16.7%	22.2%	.235
Past Psych history	29.1	48.1	70.6	94.7%	-
Low income<600KD	15.5%	7.1%	33.3%	41.1%	-
Change in life standard	1.7%	7.1%	16.7%	5.3%	.037
War was most stress	67.2%	82.1%	77.8%	100%	.026
Victim of a crime (past)	10.3%	14.3%	33.3%	31.6%	.049
Total PTSD (CAPS)	15.9±14.6	26.1±15	64.6±19.3	71±19.2	.001
Total injury	150±124	108±85	150.2±146.9	129.7±94.8	.570
Anxiety SCL-90 (1.76-4)	5 (8.6%)	5 (17.9%)	5 (27.8%)	11 (57.9%)	.001
GAD ICD-10 CIDI	0	0	2 (11.1%)	3 (15.8%)	.001
MDD ICD-10 CIDI	0	0	4 (22.2%)	2 (10.5%)	.001
Depression SCL-90R (1.76-4)	7 (12.1%)	3 (10.7%)	10 (55.6%)	12 (63.2%)	.001
Dysthymia	0	0	1 (5.6%)	0	-
OCD SCL-90R	1 (1.7%)	1 (3.6%)	2 (11.1%)	8 (42.1%)	.001
OCD ICD-10 CIDI	0	0	0	2 (10.5%)	.05
Panic ICD-10 CIDI	0	1(3.6%)	1 (5.6%)	4 (21.1%)	.001
Psychoticism	4(6.9%)	3 (10.7%)	1 (5.6%)	8 (42.1%)	.001
Somatization	2 (3.4%)	1 (3.6%)	4 (22.2%)	7 (36.8%)	.001
Hostility	1 (1.7%)	2 (7.1%)	1 (5.6%)	7 (36.8%)	.001
Anxiety	46.5±5.6	47.8±8.2	51.3±9.6	61.1±14.6	.001
Hostility	46.7±6.1	8.0±7.3	51.0±9.4	63.1±15.4	.001
Phobia	46.3±5.0	48.2±7.4	52.1±12.4	60.1±14.2	.001
Depression	45.9±6.1	47.6±8.0	53.6±8.5	60.5±14.5	.001
OCD SCL-90R	46.4±7.0	47.4±8.3	53.9±9.3	58.8±13.8	.001
Somatization	46.5±6.9	48.1±9.5	53.5±11.0	59.8±12.9	.001
Paranoid ideation	46.8±6.8	49.3±8.9	49.9±10.1	61.4±13.3	.001
Psychoticism	46.9±6.7	47.5±6.7	50.3±9.9	60.9±13.8	.001
Systolic BP	135.2±16	135.6±17.4	140.8±23.5	130.5±11.7	.008
Visual analogue after interview	1.57±.599	1.46±.582	1.87±.619	1.84±.688	.063
Life events	196.8±137.9	284.5±165.8	362.8±162.3	397.2±236.3	.001
Neuroticism	10.6±4.7	13.3±4.5	15±4.7	18.3±3.3	.001
Psychoticism	3.4±2.1	4.3±2.4	4.6±2.4	6.2±3.8	.001
Extraversion	13.1±3	13.1±3.7	11.6±4.3	10.4±4.5	.026

4. I. 3. Correlations: PTSD and No-PTSD and psychosocial variables

Table. 36. PTSD and correlations with different variables*

	PTSD and no-PTSD		
	Pearson Correlation	Sig.	N
Physical Symptoms	.430	.000	154
Daily Activities	.360	.000	152
Sleep Duration	-.247	.004	137
Depression	.439	.000	156
Anxiety	.344	.000	156
Alcohol	-.156	.052	156
Cigarette Smoking	-.179	.025	156
Psychoticism	.175	.028	156
OCD	.331	.000	156
Somatization	.285	.000	156
Hostility	.206	.010	156
Family Psychiatry History	-.158	.048	156
Total Injury Score	.017	.878	87
Panic Attacks	.197	.014	156
Blood Pressure	.086	.288	156
Pulse	-.147	.068	156
Total PTSD associated symptoms	.223	.005	156
Problems with General Health CIDI: S1-12	.591	.000	156
Torture	.067	.581	70
Diastolic Blood Pressure	.029	.723	156
Systolic Blood Pressure	.024	.769	156
BMI	.045	.577	156
WHR	.052	.522	156
EPQ: Extraversion	-.275	.001	156
EPQ: Neuroticism	.421	.000	156
EPQ: Psychoticism	.240	.002	156
Life Events Scale	.368	.000	156
SCL-90R: Positive Symptoms Distress Index	.199	.014	152
SCL-90R: positive Symptoms	.433	.000	156
SCL-90R: Global Severity Index	.435	.000	156
SCL-90R: Psychoticism	.346	.000	156
SCL-90R: Paranoid Ideation	.337	.000	156
SCL-90R: Phobic Anxiety	.363	.000	156
Cortisol	.113	.163	154
TSH	-.047	.560	154
fT4	-.018	.825	154
fT3	-.119	.143	154
Visual Analogue after the interview	.208	.011	148

***** Bonferroni correction was used for PTSD and correlations with different parameters data there were 38 variables, so the corrected p value was .0013. Any test with a p value less than .01 is significant at the 5% level

5. Discussion:

5. A. Chronic PTSD

This study found that of studied (156) war trauma survivors with physical disability the comparison between the first and second assessment: (1) (N=58 47.2%) were never diagnosed as having PTSD, (2) (N=28 22.8%) recovered from PTSD (lifetime) and (3) (N=18 14.6%) were diagnosed in the second assessment (2003) having delayed onset PTSD. While clients who continued to have PTSD during the (5) years follow up were (N=19 15.4%) these were having chronic PTSD. This result shows that PTSD has an unremitting chronic course for some patients and for others a Subclinical (sub-syndromal) phase and few has full remission. The finding that (N=19 15.4%) of clients still suffered from PTSD indicates the chronicity of this disorder. The timing between the two assessments was (5) years. Following PTSD criteria in the first and second assessment we can see that although some participants may not show the full criteria for PTSD diagnosis at the first assessment, they may suffer from a full symptoms of PTSD in the second assessment that may interfere with their daily life and that interfere with their functioning. In our sample the rate of PTSD was 38.7% and in the second phase (5) years later 30.5% had PTSD (15.9% chronic PTSD and 14.6% delayed onset). This proves our hypothesis that the prevalence of chronic PTSD is maintained in its rate during the course time for the population. These findings are consistent with other research finding that PTSD is a persistent illness (Breslau and Davis, (1992);and Kessler et al., (1995)), with more than one third of subjects failing to remit from their PTSD many years after the onset of their index episode (Kessler et al., (1995)); that the probability of full remission from chronic PTSD is low (Zlotnick et al., (1999)); and that the majority of patients who have recovered from PTSD still report sub-threshold symptoms of PTSD (Ehlers et al., (1998). Research had different views to which PTSD symptoms remain prominent in partial PTSD, because some experts speculate that it is the numbing and withdrawal symptoms of PTSD that tend to endure in chronic PTSD (McFarlane, 2000). In our sample (18/123) (14.6%) recovered from PTSD during (5) years i.e. rate of recovery (14.6) for 5 years or (2.92%) each year.

Our results of high rate of chronic PTSD in our sample (22.8% has lifetime, and 15.4% has chronic PTSD) is supported by the findings of Breslau and Davis (1992) found that (52%) of their sample with lifetime PTSD had a chronic PTSD. Chronicity of PTSD was also examined by Kessler et al. (1995) where he found that over (30%) of those with lifetime PTSD has chronic

form of PTSD. Breslau et al. (1998) found similar results in epidemiological study found that the duration of chronicity of PTSD can be of long duration, as found also by McFarlane and Papay, (1992), and Yehuda et al., (1995). The findings of chronicity of this disorder were also confirmed by other studies: Op den Velde et al., (1993), found that 22% chronic PTSD in World War II resistance fighters, and (18%) reported by Port et al., (2001). Lifetime prevalence of exposure and PTSD were (76%) and (11.2%), respectively, of lifetime cases, (62%) of them became chronic Norris (2003).

Our findings of high rate of PTSD in war survivors is different from the findings of Koenen et al (2003) who followed (1377) Vietnam veterans for (14) years. At the first assessment he found (11.8%) had PTSD and (10.5%) at Time (2) second assessment. We can explain the deference based on the differences on the type of trauma since our sample involved war survivors that have physical disability due to injury. Half of Koenen sample (5.3%) (Out of 10.5) met criteria for PTSD at both times and in our sample (15.4%) (Out of 38.2%). This gives us an indication from both studies that PTSD chronicity with time could range from (30-50%) and rate of recovery (6.3%) out of (11.8%) and in our sample (14.6%) out of (30%) both studies approximating (50%) recovery rate.

The recovery rate in our sample was (22.8%) in 5 years i.e. (4.56%) each year. Riggs et al (1995) found that (70%) of women and (50%) of men who were diagnosed with PTSD at an average of (19) days after an assault; (49%) for women and all for men recovered. Rothbaum et al (1992) found that (94%) of rape victims with PTSD after (2) weeks of the traumatic event. After (11) weeks (47%) have recovered. Breslau et al (1992) in his study found that (82%) of PTSD will continue to do so (3) months after diagnosis, (74%) after (6) months, and median time of remission (24.9) months. The decline is up to (12) months then gentle downward slope; still (28%) had PTSD after (120) months. These studies are different from our study due to different trauma and duration of follow up.

Koren et al (2001) in a (4) years follow up study examined (74) injured traffic accident victims. They could reevaluate (19/24) PTSD subjects (79%) and (39/50) Non-PTSD subjects (78%) in the (2^{nd}) part of the study. They found that (N=10, 53%) of the (19) PTSD at one-year were still suffering from PTSD after another two-year follow-up interval, while (9) recovered from PTSD during this follow-up period. Only (2) of the (39) without PTSD at one year developed delayed onset PTSD. It was concluded that the best predictor of recovery from chronic PTSD was the

initial level of posttraumatic reaction immediately after the accident, and spontaneous recovery from PTSD can occur even among patients who are delayed having PTSD. Severity of initial reaction to the trauma appears to be a major risk factor for non-remitting chronic PTSD. Koren et al (2006) indicated that "physical injury increases the risk for PTSD and there is a role for neurobiological and psychological mechanisms by which bodily injury may augment or independently contribute to chronic PTSD. They proposed three theoretical pathways through which physical injury can increase the risk for PTSD: additive, unique, and recovery impeding. In our study we found similar results that PTSD participants with mild severity of this disorder are those who recovered from PTSD in the second phase of the study, while those with severe symptoms of this disorder in the first phase, continued to have chronic PTSD. This is supporting our hypotheses that the rate of recovery in individuals with chronic PTSD is low due to the presence of the permanent physical disability which may work as a source of continuous reminder of the trauma

5. B. PTSD and Axis-I co-morbidity

In this study we hypothesized that co-morbid disorders such as depression and anxiety disorders are high with chronic PTSD and could affect the chronicity of this disorder. Marshall (2006) interviewed a sub-sample of 88 male Vietnam veterans from the National Vietnam Veterans Readjustment Study. They found that avoidance and hyperarousal cluster were associated with chronic PTSD; and these were related to prewar demographic factors (race/ethnicity, socioeconomic status, age at entry into Vietnam), comorbidity, treatment and compensation seeking, or probable severity of war-related trauma.

5. B. 1. Anxiety Disorders

In our study we found that both comorbid anxiety and depression were statistically significantly related to the chronicity of PTSD ($p<.001$). Depression was found in 27.6% of the participants and anxiety in 21.2%. This could raise the concept that comorbid disorders such as depression and anxiety disorders were significantly associated with the maintenance of PTSD. This is supported by other research the co-occurrence of comorbid disorders such as anxiety with PTSD was associated with the highest odds ratio for chronicity of PTSD compared with other comorbid disorders Breslau and Davis (1992). Others like Zlotnick et al. (1999) found that there was a very

low likelihood of full remission from chronic PTSD in patients with PTSD and a comorbid anxiety disorder. Possibly the high level of emotional arousal and affect dysregulation that accompanies an anxiety disorder may maintain or even exacerbate existing PTSD pathology, given that many symptoms of PTSD overlap with other anxiety disorders, Zlotnick et al (2004). Psychiatric risk factors for chronic PTSD in MVA survivors include a history of depression, anxiety disorders, and alcohol abuse, Blanchard and Hickling, (1997) and Koren et al. (1999).

5. B. 2. Depression

In our sample individuals with PTSD have statistically significant difference in the comorbidity of depression in association with PTSD compared to those without PTSD diagnosis: (12%) in patients who never had PTSD, (10.7%) in patient who recovered from PTSD, (55.5%) in patients with delayed onset PTSD and (63%) in patients with chronic PTSD ($P<0.001$). O'Donnell (2004), followed a group of (363) civilian injury survivors and were assessed just prior to discharge from hospital and (3) and (12) months postinjury, they found that depression in association with PTSD after (3) and (12) months are (4.7%), and (5.6%) respectively. This shows the strong association between depression and PTSD although short time follow-up between the two periods in this study compared to a longer period in our study. Depression in association with PTSD was also studied by Voloshin et al (2004). Following (165) patients with chronic PTSD for (6) to (24) months, depression was seen in these patients as (4) main types: anxious (36.6%), dysphoric (26.1%), apathic (20%) and somatoform (17.7%), this support our findings of the strong association of depression with PTSD. Fikretoglu et al (2007) in nationally representative Canadian Forces members of 8441 examined the rates, characteristics, and predictors of mental health treatment seeking in 549 of them who met the criteria for lifetime PTSD. Comorbid major depressive disorder was one of treatment seeking disorders in association with PTSD and those with comorbid depression were 3.75 times more likely to have sought treatment than those without.

5. C. Daily functioning

The delayed study showed that there was a disturbance in the daily functioning (using CIDI) with statistically significant differences between different categories of PTSD (never PTSD, delayed onset PTSD and chronic PTSD) this could be a factor for chronicity in PTSD i.e. the

lower level of psychosocial function is related to the maintenance of PTSD chronicity. Other studies also showed that functional impairment is a predictor of recovery and in another words its malfunction is also a predictor of chronicity in PTSD Leon et al. (1999).

5. D. Psychotherapy and/or Psychopharmacology

Our study showed that treatment (psychotherapy or psychopharmacology) was not significantly related to the outcome of PTSD P=0.205. Seeking therapy was not a factor that has affected the chronicity of PTSD disorder. This was also was seen by other studies Blanchard et al., (1996), Zlotnick (2004). Kessler et al., (1995) found also that treatment wasn't a factor for full remission i.e. protection from further episodes or full remission of symptoms. Zlotnick (2004) found no significant relationship between antidepressant medication (SSRI/SNRI) at any time during the first (2) years of follow-up and PTSD status, which interpreted as treatment is unrelated to recovery from PTSD. Shalev et al., 1996 believes that no treatment has been shown to be effective in achieving durable remission in chronic PTSD.

5. E. Severity of PTSD Symptoms:

Our study showed that Intrusion means in patient with delayed PTSD ($\overline{X}$ =14.55), chronic PTSD ($\overline{X}$ =13), lifetime PTSD ($\overline{X}$ =3.13), and who never had PTSD ($\overline{X}$ = 4.10). Avoidance means were: in delayed onset PTSD ($\overline{X}$ =23.62), in chronic ($\overline{X}$ =25.26), in lifetime PTSD ($\overline{X}$ =7.4), and who never had PTSD ($\overline{X}$ = 7.34). Arousal showed striking results delayed onset PTSD ($\overline{X}$ =26.75), chronic ($\overline{X}$ =27.1), lifetime ($\overline{X}$ =8.79), and who never had PTSD ($\overline{X}$ = 8.73). This shows that hyperarousal symptoms are more prevalent not only in patients with delayed PTSD but even with post traumatic patients who do no have PTSD they do have arousal symptoms. There were no statistically significant differences between chronic and delayed onset PTSD groups in intensity and frequency of total scores of PTSD (CAPS) p=0.993, total intrusions p=0.996, avoidance p=0.152 and arousal p=0.273. This proves our hypothesis that war injured survivors with Chronic PTSD have cluster of symptoms severity similar to that found patients with delayed onset PTSD after 13 years of the trauma.

Other researches found that intrusive symptoms are more prevalent than avoidant-dissociative symptoms that are more prevalent in patients with PTSD Zoellner et al (2003). Bremner et al., (1992), conceptualize that PTSD as a Phasic phenomenon, altering between arousal and avoidance states. Traumatized individuals with PTSD in our study report more arousal than dissociative or intrusive symptoms than those traumatized without PTSD. These symptoms (arousal) were not found in this severity in 1998 (1^{st} assessment in those who were not having PTSD at that time and they develop PTSD in the 2^{nd} assessment). Chronic PTSD has a lower arousal but showed same intensity of avoidant − dissociative and intrusive symptoms. Arousal symptoms in our sample were maintained at high levels which could be explained by the presence of the war physical trauma in our clients i.e. the physical injury and disability that serve as continuous reminder of the original traumatic event. This was also supported by the work of Le Doux et al (1988) in which he suggested that conditioning models suggest that stimuli present at the time of trauma become associated with arousal and function as conditioned stimuli to trigger further arousal. Although the mechanisms of sensitization are not clear, it is possible that they involve repetitive activation by trauma reminders that elevate sensitivity of limbic networks as suggested by Post et al (1995), reduce extinction of conditioned fear responses Charney et al (1993), or cause sensitization of the hypothalamic-pituitary-axis in which reduced cortisol fails to contain sympathetic activity Yehuda (1997).

Southwick et al., (1993) studying Gulf war veterans found that hyperarousal symptoms and these were more likely than other PTSD symptoms to be reported up to (2) year after the trauma. McFarlane and Papay, (1992); found that hyperarousal and avoidance/numbing symptoms were stronger predictors of later PTSD in veteran and non-veteran samples, which we found in our study.

There have been numerous studies that have indexed the relationship between initial symptoms and PTSD. A range of studies has reported that acute dissociation is predictive of subsequent PTSD, Koopman et al (1994), and Shalev et al (1997). In contrast, other studies have reported that dissociation is not strongly predictive of subsequent PTSD Dancu et al (1996). In terms of re-experiencing symptoms, there is convergent evidence that intrusive memories are not strong predictors of PTSD Perry et al (1992) and Shalev (1992). Similarly prospective studies suggest that the relationship between acute avoidance and PTSD that is complex and not strongly predictive Creamer et al (1992) and McFarlane (1992). Koren et al (2002) and Weisaeth (1989) have found that hyperarousal symptoms, such as insomnia, are predictive of PTSD). Overall,

there is little convergence across available studies to suggest that any symptom, or constellation of symptoms, is particularly predictive of PTSD. What we found in our study is supporting studies that found the intensity of PTSD symptoms years after the trauma is predictive of subsequent PTSD intensity once it developed rather than predictive of PTSD diagnosis.

5. F. PTSD and physiological parameters

In our study we found that BMI was not correlated significantly with PTSD and the mean BMI was 28.6±6.1 Kg/m² and 29.7±7.6 Kg/m², in individuals with chronic and delayed onset PTSD compared to 30.8±21.5 Kg/m², for those who never had PTSD diagnosis. Moreover obesity was found in 29%, 46.7% and 30.4% in individuals with chronic PTSD, delayed PTSD and those who do not have PTSD respectively. Vieweg et al (2006) found that the mean BMI in male veterans 30.3 ± 5.6 Kg/m², 38.2% of the veterans were overweight, 40.1% were obese and 6.4% were morbidly obese this was based on a study of 157 American veterans with PTSD. They attributed the higher BMI to the metabolic syndrome related to the multiple medications these individuals taking for medical conditions like hypertension, diabetes and not the psychotropic medications. Our results indicate that delayed onset PTSD individuals have higher BMI and more prevalence of obesity although it lacks statistical significance and it is not significantly correlated with income (p=.066) or use of psychotropic medications (p=0.72). We found among the subgroups we studied that obesity is lowest among individuals without PTSD and BMI was not significantly different and not as propose in our hypothesis. The presence of both physical and psychiatric co-morbidity and that all the subgroups in this population is traumatized may explain the results we had.

The baseline resting pulse rate in our sample did not show statistical significance in those with or without PTSD which is consistent with what Hopper et al (2006). He found that individuals with PTSD may not have elevated BHR which he attributed to the parasympathetic innervations. Beckham et al (2003) also failed to find BHR differences between veterans with PTSD and combat-exposed controls. In the other hand Buckley et al (2001) in a Meta analysis study found that individuals with a delayed PTSD diagnosis have higher resting HR relative to both trauma-exposed individuals without a PTSD diagnosis and non–trauma-exposed individuals. These findings are consistence with our hypothesis that the resting pulse rates in chronic PTSD are comparable to those individuals with trauma experience without PTSD.

The pulse pressure did not vary significantly between those with or without PTSD. Individuals with chronic PTSD, delayed onset PTSD and those without PTSD had 44.4%, 61.2% and 46.5% rate of hypertension respectively. Diastolic blood pressure was more in delayed onset PTSD mean=88.8mmHg but statistically not significant. Blanchard et al (1990) proposed that PTSD might be a risk factor for hypertension. Buckley et al (2001) concluded through a Meta analysis study that PTSD is associated with elevations in basal heart rate and diastolic blood pressure relative to comparison groups. He explained the rise in blood pressure to systemic changes in responses to stress mediated by the sympathetic branch of the autonomic nervous system, emotional priming or apprehension and probably due to direct effects on cardiovascular health e.g. alcohol and smoking. In our hypothesis that individuals with chronic PTSD had higher blood pressure values compared to individuals without PTSD; we found that in the individuals with delayed onset PTSD and not chronic PTSD that is related to the severity of PTSD cluster of symptoms.

5. G. PTSD and Social factors

In this study we found that individuals with chronic PTSD least satisfaction in social life 27.8% compared to individuals with no PTSD 43.4%. Moreover these individuals have highest rate of unemployment 22.2% compared to (lifetime PTSD 3.6%, no PTSD 19.3%), lower monthly income (<600KD) 41.8% compared to 15.5% those with no PTSD, scored having worse changes in life standards compared to individuals who never had PTSD 52.6% and 25.9% respectively. Individuals with chronic PTSD has higher scores of life events in the tear prior the interview compared to individuals with no PTSD ($\overline{X}$ =397.7) and ($\overline{X}$ =196.8) respectively. Norris et al. (2002) reviewed 160 samples of disaster victims he found that “samples were more likely to be impaired if they were composed of: youth, from developing countries, experienced mass violence, more severe exposure, female gender, middle age, ethnic minority status, secondary stressors, prior psychiatric problems, and weak or deteriorating psychosocial resources most consistently increased the likelihood of adverse outcomes. Feehan et al. (2001) indicated that the experience of trauma may have life-altering consequences in terms of social status, employment, and health, and continuing difficulties in these areas may contribute to the likelihood that a person will develop PTSD. They interviewed 374 trauma survivors; they found that unemployment is a risk factor. Brewin et al. (2000) reported in Meta-analyses three categories of

risk factors: demographic such as gender, age at trauma, and race; factors such as education, previous trauma, and general childhood adversity; and factors such as psychiatric history, reported childhood abuse, and family psychiatric; “the effect size of all these risk factors was modest, but factors operating during or after the trauma, such as trauma severity, lack of social support, and additional life stress, had somewhat stronger effects than pretrauma factors”. This is consistent with our hypothesis that psychosocial factors may maintain the chronicity of PTSD including family conflicts, loss of work and early retirement, low income, divorce, the presence of axis I disorders prior to the trauma or as co morbid disorder after the trauma.

5. H. PTSD and personality subtypes

Personality subtypes were found in our study to be more prevalent in patients with PTSD compared to other participants without PTSD diagnosis. Eysenck Personality Questionnaire (EPQ) was used in our study showed that both Psychoticism ($\overline{X}$ =3.72 SD=2.27 p<.001) and Neuroticism ($\overline{X}$ =11.51 SD=4.82 p<.001) were more prevalent with individuals with PTSD diagnosis. Moreover neuroticism and psychoticism were also correlated with PTSD cluster of symptoms (p<0.001). Casella et al (1990) examined the severity of psychopathology as assessed by EPQ for 107 Vietnam veterans with and without PTSD, who had been exposed to varying levels of combat. They found that individuals without PTSD had lower neuroticism and Psychoticism scores that are supported by our findings. Our findings about the association between neuroticism and PTSD cluster symptoms were also studied by Aidman et al (2006). They examined the relationship of extraversion, neuroticism, and impulsiveness with PTSD symptoms of avoidance and intrusion in 36 outpatients from a trauma unit at a major metropolitan hospital in Melbourne (Victoria), and 24 age-matched controls using EPQ. They found that: “Intrusion symptoms were predicted both by extraversion and more with neuroticism, avoidance symptoms were predicted by neuroticism and impulsivity correlated with intrusion symptoms but predicted them only in the trauma group. Their findings is support Gray's model of dispositions influencing responses to trauma, suggesting that impulsive (extroverted) neurotics are more vulnerable to posttraumatic stress than introverted ones.

Reviewing the literature there are evidence to support our findings about the association between neuroticism, psychoticism and PTSD symptomatology. Brodaty et al (2004) studied factors that are associated with psychological morbidity in PTSD in (100) holocaust survivors who were

randomly selected from a convenience sample of 309 respondents to a survey of Jewish persons aged 60 years and older living in the community in Sydney. They found that older age, experience of more severe trauma, use of immature defense mechanisms and higher neuroticism were associated with significant PTSD and psychological morbidity; severity of trauma was associated with PTSD and with more severe psychological morbidity. To investigate the contribution of personality and peritraumatic dissociation in the development of PTSD Holeva et al (2001) examined 265 traffic accidents (RTA) individual within 2-4 weeks (Time 1) of the accident and again between 4 and 6 months (Time 2). They found that although neuroticism, psychoticism, and peritraumatic dissociation were significantly correlated with PTSD symptoms, only the personality dimensions were independent and significant predictors of subsequent PTSD in a logistic regression. Malta et al (2002) found that prevalence of at least one personality disorder in patients with PTSD was (13.3%) with the majority (52.4%) presenting with obsessive-compulsive personality disorder. Persons with a personality disorder were significantly more likely to be diagnosed with PTSD at (1) year follow-up evaluation. For persons diagnosed with PTSD at the initial assessment, those with a personality disorder were significantly less likely to remit by (1) year Malta et al (2002), they concluded that the presence of a preexisting personality disorder may increase the risk of chronic PTSD and impede remission. This is supported by our study that participants with chronic PTSD they have more prevalence of personality subtypes than those with other PTSD subscales discussed in this study. Bollinger et al., (2000) reported that cluster C personality disorders were the most prevalent in patients with PTSD, which is consistent with the reported high rates of cluster C personality disorders co-morbidity with PTSD Southwick et al. (1993).

6. Conclusions:

War in general may influence the rate of acute PTSD in the affected population and it may continue to influence the rate of chronic PTSD in the affected people. These patients may pass unnoticed to the health care system, but they are there in the community, and PTSD may develop in a substantial number of the population with time. Some people do not develop PTSD although they were injured, some develop acute type of PTSD and they recover from it, while others do not and continue to have chronic type of PTSD. Some they develop a late onset type of PTSD. The following are the characteristics of participants who developed chronic PTSD:

1. War injured survivors with Chronic PTSD have cluster of symptoms severity higher than those in patients with delayed onset PTSD after 13 years of the trauma.

2. The prevalence of chronic PTSD is maintained in its rate during the course time for the population.

3. Factors that may maintain the chronicity of PTSD includes:

A. Personality subtypes
B. Life events
C. Anxiety
D. Depression
E. Other psychological symptoms e.g. hostility, phobia, OCD, somatization and cognitive problems such as psychoticism

4. The severity of physical injury was not found to be a factor in chronic PTSD compared to other PTSD subtypes.

1. The rate of recovery is low from PTSD related to war injuries compared to other trauma

2. Taking treatment (psychotherapy and/or Psychopharmacology) did not change the prevalence of PTSD probably to the relapse.

3. Chronic PTSD patients had more prevalence of PTSD associated symptoms included in CAPS includes: guilt not taking an action, survivors guilt, homicide, disappointed with others, hopelessness, memory problems, depressed and overwhelmed.

4. Intrusions, avoidance and arousal are PTSD cluster of symptoms more predictive of future development of PTSD.

5. PTSD diagnosis at one stage is not predictive of future development or chronicity of PTSD in future.

Chapter V. Cortisol hormone in Chronic PTSD

1. Introduction:

Posttraumatic stress disorder PTSD develops after experiencing or witnessing an extreme and overwhelming traumatic event that is perceived by the individual as life threatening with obvious helplessness.

The trauma, as described in the DSM-IV-TR APA (2000), is characterized by serious threat to life, physical integrity, or a serious harm to family member. Based on DSM-IV-TR criteria, PTSD can be classified as follows:

1. Acute PTSD: from onset the duration of PTSD symptoms more than 1 month and less than 3 months.
2. Chronic PTSD: from onset the duration of symptoms more than 3 months.
3. Delayed Onset PTSD: The onset of PTSD symptoms more than 6 months, and the duration of symptoms 1 month or more.

Christopher (2004) had broader view of the trauma when he reached the following conclusions: "(1) Stress is best understood as a prerational form of biopsychological feedback regarding the organism's relationship with its environment; (2) The normal outcome of traumatic stress is growth, rather than pathology; (3) Most psychopathology is a function of the maladaptive modulation of the stress response; (4) Trauma always leaves the individual transformed on a biological, as well as psychological, level; (5) The general biological process underlying stress responses is universal, but the specific dynamics are always a function of the unique sociocultural environment and psychological makeup of the individual; (6) The biology underlying stable psychopathological symptoms may change even as the psychological symptoms remain the same; and (7) Rationality is humanity's evolutionarily newest and most sophisticated stress-reduction behavioral mechanism, and the most important aspect of restoring psychological health to the trauma victim".

The lifetime prevalence of PTSD is 7.8 %, with twice the prevalence in women compared to men (10.4 vs. 5.0). Women have greater exposure to trauma than men (other than war) (Kessler et al, 1995). Furthermore, war veteran survivors have a high prevalence of PTSD compared to other non- war survivors. Kulka (1990) reported that 25% of US men and women veterans of 1990 Gulf war were diagnosed with PTSD. The physical exposure component of the trauma was the

most important factor for PTSD development i.e. witnessing death or injury of others or threat of physical injury (Kessler 1995).

Co-morbid psychiatric disorders may develop before, during or after PTSD development. The psychiatric comorbid disorders include major depressive disorder, panic disorder, substance use, phobias, obsessive-compulsive disorder, and somatization disorder.

There are psychological and biological theories that attempt to explain PTSD symptoms. Charney et al (1993) explain the neuroendocrine and neurochemical theories that could clarify the pathogenesis and symptomatology of PTSD. The noradrenergic sensitization could explain hyperarousal symptoms, opiod dysfunction may be the cause of numbing symptoms, and dopamine dysfunction may contribute to hypervigilance symptoms and cortisol affecting the hippocampus could explain problems in memory.

PTSD symptoms develop at different times and they behave during the course of the disease in different ways. Onset of symptoms begins at the time of exposure to the traumatic event and continues throughout the course of the disease. The first symptom to appear is hyperarousal and which may continue for many years after the first exposure although its intensity will be less than in the first episode. Bremner et al (1996), using a structured interview to assess PTSD and alcohol and substance abuse, as well as other factors such as life stressors in 61 Vietnam combat veterans. They found that 15% of the patients had developed PTSD during their combat tour, 62% met criteria for PTSD within 2 years after the end of their combat tour, and 13% had met full PTSD criteria more than 10 years after the Vietnam War. There were 56 patients who were able to rank the order in which their symptoms developed first: 63% reported a symptom from the hyperarousal cluster as being the first to develop, 32% reported a symptom from the avoidant cluster as being the first symptom to develop, and only 5% reported a symptom from the intrusive cluster as being the first symptom to develop. Bremmer et al (1996) hypothesized that the development of hyperarousal as the first cluster of symptoms was related to the endocrine abnormality triggering the cascade of PTSD symptoms.

Patients with a PTSD diagnosis exhibit different biological response to trauma than the usual stress related biological response. There is accumulated evidence supporting the importance of neuroendocrine causes playing an important role in the pathogenesis of this disorder. Thus, there is increasing evidence that PTSD is not simply an abnormal response to a traumatic stress, but

rather that it represents a cascade of multiple biological events that causes an abnormal dysfunction in the central nervous system and in the endocrine system which result in this chronic disorder. Patients with PTSD diagnosis exhibit different biological response to trauma than the usual stress related biological response.

I will concentrate the discussion on the neuroendocrine factor and its relation to other factors in the pathogenesis of PTSD.

2. Brain structures in PTSD:

The brain and the endocrine structures are the first to be affected as sequelae of the traumatic event. The two main brain structures involved in the pathogenesis of PTSD are the amygdala and the hippocampus. The amygdala receives neural connections from the thalamus and the cortex, and sends efferent fibers to the brainstem, hypothalamus, and striatum. These neural circuits that are concerned in the process of PTSD reaction involve the autonomic, neuroendocrine and motor systems. These are involved in fear conditioning and extinction Charney et al. (1993). The hippocampus keeps the memories of the traumatic event, and mediates learned responses to a group of traumatic signals. It receives neural connections from and sends efferent fibers to both amygdala and the cerebral cortex Charney et al. (1993). These two structures are involved in the pathogenesis of PTSD. Studies using Positron Emission Tomography (PET) scan and or Magnetic Resonance Imaging (MRI) show an increased right amygdala activity and a shrunken hippocampal volumes which correlate with severity of trauma experience or memory problems Rauch et al (2000) and Lieberzon et al (1999-a). This is supported by the Meta analysis of Kitayama et al (2005) reviewing studies in adults with chronic PTSD, to clarify the role of hippocampal structural changes. Nine studies with a total of 133 adult subjects with chronic PTSD, 148 healthy controls, and 53 traumatized controls were included in this meta-analysis. They found that there was significantly smaller volume in both right and left hippocampus in adult subjects with chronic PTSD in comparison with both healthy controls and traumatized controls. There are several possible explanations for smaller hippocampal volume in PTSD: increased glucocorticoid secretion, inhibition of neurogenesis, reductions in brain derived neurotrophic factor, and other factors, such as alcohol abuse, substance abuse, or depression, all may account for smaller hippocampal volume in PTSD. Gilbertson et al (2002) studying monozygotic twins discordant for trauma exposure found a pre-existing smaller hippocampal volume which constitute a risk for the development of PTSD, and it is negatively correlated with PTSD severity.

The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in the pathogenesis of PTSD. This involves the sensitization of the neurotransmitters that play a role in the symptomatology of PTSD and involve noradrenalin, dopamine, opioid and serotonin systems. Excess noradrenalin release during stress explains increased autonomic activity in PTSD patients. This may lead to post-synaptic down-regulation of adrenergic receptors. PTSD hypervigilance symptoms are mediated by the sensitized dopamine system. Opioids are released

during trauma. The HPA axis is also sensitized in patient with PTSD Charney et al. (1993) and Yehuda et al (1998-a). Serotonin plays an important role in PTSD patients as PTSD involves an intense fear during the traumatic event, Hensman et al (1991). Serotonin also enhances the release corticosteroids, Joseph et al (1983).

The hippocampus which is essential for learning and consolidation of memory was found to be of low hippocampal volume in patients with PTSD Gilbertson et al (2002) compared with healthy controls using MRI. Moreover learning and memory impairments in PTSD patients were also attributed to low hippocampal volume using structured neuropsychological testing and PET scans. The brain's norepinephrine system is hyperactive in PTSD, which may explain hyperarousal symptoms of PTSD. Gilbertson et al (2002) explain that low hippocampal volume in that a smaller hippocampal volume constitute a pre-existing vulnerability factor for pathological response to stress studying monozygotic twins as stated above and the low rates of cortisol are there at the time of the trauma exposure. More over the rapid outpouring of glucocorticoids (cortisol) from the adrenal cortex at the time of stress have been shown to have neurotoxic effects on the hippocampus in laboratory animals. There is no proof that the high levels of corticosteroids that gush through an individual under acute stress are damaging to the hippocampus. Although cortisol levels in patients with PTSD measured years after the trauma was observed to be low, yet the hormone levels were not measured at the time of trauma, which could be high. Others believe that hippocampal atrophy in PTSD patients could be caused by substance abuse problems and not PTSD, or it could be that the hippocampus is smaller than normal before the traumatic stress, which predisposes a person to PTSD, Charney et al (1993).

Patients with PTSD have impaired performance on neuropsychological tests of verbal and visual memory, Bustamante et al (2001). Studying 8 firefighters with PTSD and 8 participants without PTSD Shin et al (2004) showed that an abnormally elevated hippocampal activity in PTSD might be consistent with reduced efficiency of the hippocampus during the performance of an explicit memory task and/or with impaired integrity of inhibitory interneurons within the hippocampus. In this study, they found that the relationship between hippocampal function and volume in PTSD appeared to be complex. The PTSD group exhibited abnormal modulation of regional cerebral blood flow (rCBF) in the left hippocampus during an explicit memory task (driven primarily by elevated rCBF in the Low Recall condition), greater rCBF in hippocampus (bilaterally) across conditions, and smaller right (and a trend for smaller left) hippocampal volumes. PTSD symptoms were positively correlated with rCBF in the hippocampus and

parahippocampus. However, rCBF abnormalities in the hippocampus did not necessarily reflect a functional compensation for reduced hippocampal volumes, because (1) hippocampal rCBF changes did not correlate with hippocampal volumes and (2) statistically controlling for hippocampal volumes did not eliminate the group difference in rCBF increases, Shin et al, (2004).

Anxiety may be mediated by hyperactivity of the septohippocampal system in which an abnormally functioning hippocampus and medial prefrontal cortex fail to inhibit a hyperresponsive amygdala. Individuals with PTSD do not exhibit impairment on all measures of memory ability. The etiology of functional and/or structural abnormalities in PTSD is far from clear. Hippocampal abnormalities in PTSD are due to stress-induced neurotoxicity, and there is some support for the notion that hippocampal abnormalities may be present in individuals prior to trauma exposure and act as a vulnerability factor for the development of PTSD. Decreased hippocampal volumes found in patients with other psychiatric disorders like major depressive disorder may be due to association with previous traumatic experience as shown by recent study has reported decreased hippocampal volumes in depressed women with histories of childhood abuse, but not in depressed women without such histories (Bustamante et al, 2001).

3. Biochemical changes in PTSD:

In the normal stress response, a burst of sympathetic nervous system activity constitutes the immediate response. Activation of the hypothalamic-pituitary-adrenal (HPA) axis occurs shortly thereafter. Cortisol is the final mediator of the HPA response, and there is an elevation of cortisol in the normal stress response. Patients with PTSD have a distinct biochemical body changes which differentiate them it from those with other psychiatric disorders. Studies have reported the following biochemical changes. Cortisol level is low (although this finding is not consistent in all studies), there is hypersuppression of cortisol in dexamethasone suppression test, the urine secretion of cortisol is low, the catecholamine secretion is high, the norepinephrine/cortisol ratio is increased, the brain catecholamine levels are low, the corticotropin-releasing factor (CRF) concentrations are high, and there is an increased sensitivity of the HPA axis with a strong negative feedback of cortisol due to a generally increased sensitivity of cortisol receptors, Yehuda (2001).

The body produces cortisol, epinephrine and norepinephrine (NE), vasopressin, oxytocin and Opioids hormones in response to acute stress. Because of desensitization in chronic stress the effectiveness of these hormones is inhibited, Axelrodet al (1984).

The NE is secreted by the Locus Coeruleus (LC) and distributed through much of the CNS, particularly the neocortex and the limbic system, where it plays a role in memory consolidation and helps initiate fight/flight behaviors. Adrenocorticotropin (ACTH) is released from the anterior pituitary, and activates a cascade of reactions, eventuating in release of glucocorticoids from the adrenals, Van Der Kolk (1994). The precise interrelation between HPA axis hormones and the catecholamine as biological reactions in acute and chronic stress responses is not entirely clear, but it is known that stressors that activate NE neurons also increase CRF concentrations in the LC, while intracerebral ventricular infusion of CRF increases NE in the forebrain Van Der Kolk et al (1994).

Yehuda et al (1998-b) proposed that in acute stress glucocorticoids and catecholamines may adjust each other's effects, cortisol helps regulate stress hormone release via a negative feedback loop to the hippocampus, hypothalamus and pituitary and normalize catecholamine-induced arousal in limbic midbrain structures in response to stress. In chronic stress, however, a negative feedback loop is activated resulting in: 1) a decreased resting glucocorticoid levels in chronically stressed, 2) decreased glucocorticoid secretion in response to subsequent stress, and 3) increased concentration of glucocorticoid receptors in the hippocampus.

Yehuda et al (1991) have suggested that increased concentration of glucocorticoid receptors could facilitate a stronger glucocorticoid negative feedback, resulting in a more sensitive HPA axis and a faster recovery from acute stress. Chronic exposure to stress affects both acute and chronic adaptation by permanently altering how an organism deals with its environment on a day-to-day basis, and interfering with how it copes with subsequent acute stress.

3. A. Neuroendocrine:

There are multiple endocrine abnormalities, such as adrenaline and noradrenalin, cortisol, thyroid, and growth hormones, have been found in patients with PTSD. Yehuda et at (1998-b) thought that startle response symptoms would continue as the PTSD symptoms are active especially in patient with chronic stress. Re-experiencing of the traumatic and the autonomic hyperarousal symptoms could be explained by the down-regulation of alpha 2 adrenergic receptors of the noradrenergic system which will cause an increase in noradrenalin levels and enhanced LC activity. These patients have an increase in the levels of CRF in the cerebrospinal fluid, which in turn reflects the increase levels of these hormones, i.e. plasma concentration of both adrenaline and noradrenalin. Hyperarousal symptoms could also be partly explained by activation of the serotonergic system, increasing serotonin level which affects the control of the function of septohippocampal behavioral inhibition system. Emotional numbing and amnesia could be explained by a high endogenous opiate secretion (Yehuda et al, 1998-b).

3. B. Cortisol:

The literature to date has shown different findings regarding the levels of cortisol: both diurnal and the 24 hour urinary cortisol. Some have found low baseline, others normal range and some have found an elevated baseline level of cortisol hormone in chronic PTSD patients. We will outline a summary of the current view about the relation of cortisol in PTSD.

Most studies on PTSD patients had shown low cortisol, although a few studies have shown high or normal cortisol levels. High cortisol levels have deleterious effects on the function and structures of the hippocampus, and prefrontal cortex (Marshall et al, 2002). CRF release in patients with PTSD increases both ACTH and cortisol. Furthermore, ACTH increases the release of both cortisol and dehydropeiandrosterone (DHEA) which acts on up-regulating HPA, and has an antiglucocorticoid effect. The role of cortisol is significantly correlated with CRF and ACTH.

Trauma may have an effect on the HPA axis regardless of PTSD development. Bremner (2005) stated that studies in animals and humans have shown that biological stress response systems, including norepinephrine and cortisol, are affected in both the acute and chronic stages of the trauma response especially memory areas, including the hippocampus, amygdala, and prefrontal cortex. Offner et al (2002) prospectively evaluate the cortisol response and determine the

incidence of occult adrenal insufficiency after severe trauma over an 18-month period, in 22 severely injured patients admitted to the surgical intensive care unit. They conclude that serum cortisol levels increased immediately and gradually returned towards normal after severe trauma. Occult adrenal insufficiency was common (60%) in this small group of severely injured patients.

Yehuda et al (2002-a) have stated that the 24-hour urinary excretion of cortisol is low, high or normal. 24-hour urinary excretion of cortisol is not related to the high CSF CRF levels observed in PTSD patients. The increased levels reported in PTSD patients could be due to comorbid disorders or type of trauma, and hyper-responsiveness of the HPA axis. Studies measuring the circadian rhythm of cortisol levels in PTSD patients compared to controls showed low mean levels and reduced levels at several points during the day. The lowest points were early morning and late night and that could explain the failure to observe differences in cortisol levels obtained at times when cortisol levels are not typically altered. To show the low levels of cortisol in PTSD Aerni et al (2004) suggested that giving low-dose cortisol (10mg/day for 1 month, with 3 months observation period) to three patients with chronic PTSD in a double-blind, placebo-controlled, crossover design study. He showed that cortisol treated patients had improvement in PTSD symptoms. Yehuda et al (2002-a) have suggested that there may be a transient elevation in cortisol which is short-lived because of efficient containment of ACTH release as a result of enhanced glucocorticoid receptor activation.

Mason (2002) suggested a psychogenic basis for cortisol level alterations in PTSD. The findings do not support the concept of either "hypocortisolism" or "hypercortisolism" in PTSD, but rather a central regulatory dysfunction of the HPA axis that is characterized by a dynamic tendency to overreact in both upward and downward directions.

Yehuda (2006) stated that cortisol levels are not a useful diagnostic marker for PTSD. She had summarized the current opinion the role of cortisol in PTSD. The biologic alternations may predate PTSD, the specific biologic markers present prior to trauma exposure, that glucocorticoid levels may be lower in PTSD, lack of containment of sympathetic nervous system. Cortisol alternations in PTSD are different from those observed in stress. The paradoxical findings of cortisol reflect the importance of differences regulation of HPA axis reflecting adaptation s to fundamental alternations in glucocorticoid responsiveness. What is uncertain as Yehuda (2006) stated that: this alternation confined to specific subgroup of PTSD, glucocorticoid responsiveness and HPA alternations, PTSD symptoms improvement manipulated by HPA axis regulation.

Yehuda (2006) reviewed literature and found that ambient cortisol levels were significantly lower, higher or not significantly different. This is not suggestive of endocrine pathology. The following variables she described may explain variability in cortisol measurements: age, gender, body weight, height, metabolism, medical illness, mood, substance use, nicotine, and environmental stress, sleep cycles activity levels and menstrual status. Factors that can contribute to the stability of the results includes: homogeneous sample, measurements under controlled conditions and sample size. Other important factors related to the methodological details includes: sample collection, processing of biological assays and how cortisol levels were determined. There is a role to the sympathetic adrenal medullary and HPA axis to regulate response to stress: lower cortisol level to the "focal" trauma and elevated levels in those who developed PTSD and subjected to response provocation. Low cortisol levels with PTSD were found to have negative correlations with: avoidance and hyperarousal, duration since the trauma, depression, symptom severity and medial temporal lobe perfusion. It was also seen that there is positive correlation between cortisol level with hippocampal N-acetylaspartate NAA marker of cell atrophy (trophic effect of cortisol rather than neurotoxic effect), and perfusion of anterior cingulated perfusion in PTSD and negative correlated in no-PTSD individuals reflecting an augmented hippocampal effect secondary to increased sensitivity of brain glucocorticoid receptors which account for the inverse relation despite equal cortisol levels in PTSD and no–PTSD groups.

Studies reporting normal values may have specific methodolical reasons for differences as opposed to random variation. The finding of levels that are not elevated is an important positive finding showing the pathophysiologic significance of insufficient glucocorticoid signaling in stress related neuropsychiatric disorders Yehuda (2006). A recent study on Vietnam veterans with sample size of about 2400 found low 8:00 am cortisol in PTSD compared to non-PTSD and the actual difference between the groups is only 4% Yehuda (2006). She considered that pre- or peritraumatic cortisol levels facilitate development of PTSD, and low cortisol levels may only present in trauma survivors with specific risk factors (specific subtype of PTSD). One major difference she found between PTSD and no-PTSD was that PTSD individuals have lower cortisol levels late night and very early a.m. time which normalize in the morning, these results were replicated by another study. This implies a potential for a greater reactivity of the system in PTSD in part is a function of the range of cortisol released over the diurnal cycle which is PTSD was greater.

Yehuda (2006) concluded in her review of role of cortisol in PTSD that there are different HPA axis alternation associated with different aspects of PTSD including development of this disorder even before the exposure to focal trauma. She considered that HPA axis is dynamic system that may show transient increase under certain environmental conditions, and other experts have an important observation that HPA response is in the normal range and do not reflect endocrinopathology. She thinks that future studies should pay consideration to: developmental issues, individuals' differences, and the longitudinal course of the disorder.

3. C. Catecholamine in PTSD

Catecholamine levels are high in PTSD patients which seem to be unrelated to low cortisol levels. ACTH levels in PTSD patients are surprisingly normal despite lower cortisol levels, which could be due feedback preventing ACTH increase (Yehuda et al, 2002-b). According to Yehuda et al, (2002-b) the studies which have reported higher cortisol levels at the same time found a lower ACTH levels. Giving PTSD patients cholecystokinin tetrapeptide (CCK, a strong stimulator of ACTH) leads to an attenuated elevation of ACTH which gave a rise in cortisol level which declined rapidly from its peak compared to controls. This indicates that this rapid decline is consistent with a sensitive negative feedback inhibition secondary to increased glucocorticoids receptor activity in the pituitary

4. The Dexamethasone suppression test (DST) in PTSD

Using DST it was shown that patients with PTSD have hypersuppression of cortisol i.e. enhanced negative feedback Spivak et al (1997). This may be explained by the increased secretion of CRF which leads to enhanced negative feedback, and an increase in glucocorticoid receptors GR and subsequent decreased response to stress. It is the low observed levels of this hormone in patients with PTSD that it is thought to be responsible for the continuation of the symptoms observed in PTSD patients. Spivak et al, (1997) found that trauma survivors with PTSD have higher levels of noradrenalin and lower levels of cortisol which ultimately reduces the body's stress responses, and may interfere with the body's ability to restore itself fully in the aftermath of a trauma.

5. Adrenal gland in PTSD

The normal range of cortisol level indicates that PTSD patients have no hypoadrenalism. Metyrapone (which prevents adrenal steriodogenesis) test was used to test the hypersuppression of HPA axis in patients with PTSD. It was found that there is a complete reduction of cortisol levels in both PTSD and controls but a higher increase in ACTH and 11-deoxycortisol in PTSD patients. This increase could be explained by increased suprapitutary activation (suprapitutary release of ACTH as a direct hypothalamic CRF stimulation) with a strong feedback inhibition even in the absence of hypersecretion of CRF (Yehuda et al, 2002-b).

6. Hypothalamic-Pituitary-Adrenal axis (HPA)

Pituitary adrenocortical alternations may not be a universal response in PTSD patients. Yehuda et al (2002-b) suggest that only a proportion of participants in a particular group may exhibit evidence of such alterations. In a study by Hockings et al (1993) blocking inhibition of CRH using naloxone in PTSD patients resulted in an increase in ACTH and cortisol level in 6 out of 13 patients with PTSD, with the other 7 PTSD patients having the same results that of 7 controls. The HPA axis response alterations may be due to long-term exposure to stress. Heim (2000) suggested that HPA axis and autonomic nervous system hyper-reactivity (due to CRF hypersecretion) is a persistent consequence of childhood abuse that may contribute to the diathesis for adulthood psychopathological conditions. The role for CRF receptor antagonists in the prevention and treatment of psychopathological conditions related to early-life stress was proposed.

7. Pituitary gland in PTSD

Yehuda et al (2002-c) have tested the role of the pituitary gland in PTSD patients. To test pituitary sensitivity, exogenous CRF was given to patients with PTSD. PTSD patients, with low cortisol level to begin with, have blunted ACTH response which could be due to hyposensitivity of pituitary due to increased negative feedback inhibition secondary to increased glucocorticoid receptors number or sensitivity.

8. Cortisol Receptors:

Yehuda et al (2002-c) postulated that there is an increased negative feedback inhibition due to increased receptor sensitivity. The lymphocyte and glucocorticoid receptors have been shown to increase in number and sensitivity due to low cortisol levels in PTSD patients compared to non PTSD participants. Glucocorticoid receptors mediate the effects of glucocorticoid. With the hypersuppression by dexamethasone there is a decline in the number of cytosolic lymphocyte receptors due to enhanced negative feedback inhibition.

9. Potential covariates

Yehuda (2006) in her review found that ambient significantly lower, higher or not significantly different levels of cortisol were all reported in the literature. This is not suggestive of endocrine pathology. The following variables she described may explain variability in cortisol measurements: age, gender, body weight, height, metabolism, medical illness, mood, substance use, nicotine, and environmental stress, sleep cycles activity levels and menstrual status. Golier et al (2006) examined plasma cortisol and lymphocyte glucocorticoid receptor number were measured at 08:00 h on two consecutive days, before and after administration of 0.5mg of DEX at 23:00 h in 42 male Gulf War veterans (14 without psychiatric illness, 16 with PTSD only, and 12 with both PTSD and MDD) and 12 healthy male veterans not deployed to the Gulf War or another war zone. They found that alterations in neuroendocrine function are associated with deployment to the Gulf War and post-deployment musculoskeletal symptoms, but not PTSD.

Physical symptoms were reported in Gulf war veterans including multiple symptoms such as fatigue, joint pain, muscle pain, memory disturbance, gastrointestinal and respiratory symptoms Murphy et al. (1999). These symptoms have no organic evidence explaining their pathogenesis Karlinsky et al. (2004). The only symptoms that were attributed to alterations in the autonomic nervous system or immune system are the cardiovascular symptoms; (Haley et al., 2004). Physical health symptoms in Gulf war Veterans are also notably associated with psychiatric symptoms Barrett et al. (2002). They found that percent suppression of cortisol to DEX was significantly associated with musculoskeletal symptoms (r=0.44, df=32, p=0.009), and not significantly related to mood-cognitive symptoms, fatigue controlling for weight, smoking status and group. Moreover they found that percent cortisol suppression was not associated with total CAPS score controlling for weight, smoking status or MDD diagnosis and cortisol suppression

was not related to PTSD. Rather cortisol hypersuppression was associated with musculoskeletal symptoms, and this association suggests that altered regulation of the HPA axis may underlie some of the medically unexplained symptoms in Gulf War veterans. They also stated that their results was also reported with fibromyalgia and chronic fatigue suggesting the possibility of a common basis for Gulf War-related health symptoms and these multi-symptom stress-related illnesses or the presence of some psychological or biological factor common to these conditions and to PTSD.

Golier et al (2006) With respect to the biological dependent variables, current smokers (n=15) differed from non-smokers (n=39) only on pre-DEX GR number (1976.3 per cell (±628.4) vs. 2643.1 per cell (±1185.7); $F(1,52)=4.25$, $p=0.04$). Weight was significantly associated with pre-DEX cortisol levels ($r=-0.32$, $n=54$, $p=0.02$). The relationship of weight and smoking status with the dependent variables did not differ among the groups; therefore, both were used as covariates in all analyses. Neither age nor past history of substance abuse were associated with the dependent variables and accordingly were not used as covariates.

Olff et al (2006-a) examines the relationships between PTSD, posttraumatic MDD, smoking and levels of circadian cortisol 2-3 years postdisaster in survivors of the Enschede fireworks disaster: 38 healthy survivors, 40 subjects with PTSD, and 17 subjects with posttraumatic MDD. Salivary cortisol samples were collected: immediately upon awakening, 30 min after awakening, at noon, and at 10 p.m. Quantity of smoking was measured through self-report. They found that salivary cortisol concentrations were higher in smoking subjects, and subjects with posttraumatic MDD had a flatter diurnal cortisol curve compared to subjects with PTSD or healthy survivors. In survivors with PTSD and healthy individuals the usual dynamic pattern of increase in cortisol past awakening was present, this was not observed in posttraumatic MDD. Posttraumatic MDD individuals tended to use more tobacco per day, and the cortisol group differences could only be revealed when adjusted for quantity of smoking. They conclude that smoking, may be an important palliative coping style in dealing with posttraumatic arousal symptoms, and it seems to mediate the relationship between traumatic stress and the HPA-axis.

Santa et al (2006) examined the HPA axis response to a classic physical stress task, the Cold Presser Task (CPT), in individuals with PTSD, alcohol dependence and PTSD, and controls. The tests were conducted at 08:00h plasma adrenocorticotrophin hormone (ACTH), cortisol, and subjective stress at baseline and five post-task time points in 3 groups: 31 controls, 25 subjects with PTSD as a result of an index trauma during childhood (i.e. before age 18; n=25), and 33 subjects with PTSD as a result of an index trauma as an adult. They found that a substantial number of individuals in the childhood trauma and adult trauma groups had a diagnosis of alcohol dependence. The ANOVAs failed to identify any significant alcohol-related main effects or interactions for cortisol (all *F*'s<1.0), ACTH (all *F*'s<1.0) or stress (largest *F* [5,245] =2.1, *p*=.09). They conclude that regardless of the presence or absence of comorbid alcohol dependence, subjects with childhood trauma had lower cortisol at baseline and at all post-task measurement points and did not demonstrate the decrease in cortisol over the course of the 2h monitoring period seen in subjects with adult index trauma and controls.

Wessa et al (2006) stated that there is inconsistent empirical evidence about the altered function of the HPA axis in PTSD. They measured salivary cortisol levels at seven intervals from awakening until 8 PM in 29 trauma-exposed subjects and 19 with PTSD, 19 without PTSD and in 15 non-exposed controls. They found that while the three groups did not differ with respect to their first cortisol level immediately after awakening, the expected cortisol increase to awakening 15–60 min later was significantly lower in PTSD patients compared to non-PTSD subjects and healthy controls. This effect remained stable when trauma-exposed subjects with comorbid major depression were excluded from the analysis. A significant negative correlation between the overall cortisol secretion and overall PTSD symptomatology and hyperarousal symptoms was found. Covariates such as age, sex, intake of contraceptive medication, cigarette smoking and wake-up times were tested in this study. These covariates showed no significant impact on the reported group effects or interactions, neither with regard to the morning profile nor overall cortisol secretion. In addition, one-way ANOVAs of the wake-up-times and the sleeping hours during the night before cortisol sampling showed no significant differences between the three groups (wake-up times: $F(2,60)=2.39$; ns; sleeping hours: $F(2,60)=0.72$; ns).

Yehuda et al (2004-a) evaluated cortisol suppression following 0.5 mg of dexamethasone in 52 trauma survivors with PTSD, MDD, both, or neither disorder, and in 10 subjects never exposed to trauma, in order to examine interactions between diagnosis and trauma history on cortisol negative feedback inhibition. They found that PTSD was associated with enhanced cortisol suppression in response to dexamethasone. The presence of a traumatic event prior to the "focal" trauma had a substantial impact on cortisol suppression in subjects with MDD. Such subjects were more likely to show cortisol alterations similar to those associated with PTSD, whereas subjects with MDD with no prior trauma were more likely to show alterations in the opposite direction, i.e. relative non-suppression. They conclude that cortisol hypersuppression in PTSD appears not to be dependent on the presence of traumatic events prior to the focal trauma. However, prior trauma exposure may affect cortisol suppression in MDD. This finding may have implications for understanding why only some depressed patients show non-suppression on the DST.

Table 1 summarizes the findings from the literature cortisol levels in patients with PTSD. The division of low, normal or high was based on what was reported in that reference about the level of cortisol in the participants.

Table 1. Plasma morning cortisol levels in participants with PTSD and comparison participants
Cortisol levels (μg/dl), (Number of participants)

Study	Trauma survivors with PTSD	Trauma survivors without PTSD	Normal comparison participants	Psychiatric comparison participants	Status
Jensen (1997)	4.6(7)	-	8.9(7)	9.9(7)	Low
Boscarino (1996)	17.7(293)	18.4(2197)	-	-	Low
Kanter (2001)	7.6(13)	-	10.6(16)	-	Low
Yehuda (1993-a)	14.3(21)	-	15.1(12)	-	Low
Yehuda (1995-a)	12.7(14)	16.4(12)	15(14)	-	Low
Yeh1uda (1996)	11.6 (15)	-	14.2(15)	12.2(14)	Low
Kellner (1997)	7.8(8)	-	13.3(8)	-	Low
Yehuda (1991)	14.3(15)	-	14.9(11)	-	Normal
Halbreich (1989)	7.7 (13)	-	7.3 (21)	12.3 (23)	Normal
Thaller (1999)	21.6(34)	-	21.4(17)	-	Normal
Liberzon (1999-b)	12.1 (17)	7.9(11)	9.3(14)	-	High
Hoffman (1989)	18.2 (210)	-	14.1(20)	-	High

10. Hypotheses:

A. Patients with chronic PTSD have low cortisol levels, which are compared to those with delayed onset PTSD or lifetime PTSD.

B. Patients who completely recovered from PTSD may have normalized their cortisol levels whereas patients with partial recovery, cortisol levels changes may persist.

C. Co- morbid psychiatric disorders with PTSD may have an impact on cortisol levels.

D. Degree of disability, age, and duration and severity of PTSD symptoms may have an effect on cortisol level i.e. hyperarousal associated with PTSD is episodic. Differences in cortisol response among those with or without PTSD are most apparent in the context of even minor stressful stimuli that provoke the differential response and less apparent in subjects who have not been exposed to recent stressors.

11. Results:

The following is summary of the results; more details of the results are in the appendices.

11. A. Socio-demographic

11. A. 1. Age:

The age of participants ranged from 28 years to 72 years with a mean of 41.79 years (SD= 8.92). The age distribution showed that 28.8% of the sample was less than 35 years of age and 5.8% of the sample was above 56 years of age.

The sample was divided into two groups Table 2 PTSD (30%) and no-PTSD (70%) groups based on the CAPS questionnaire. The no-PTSD group was composed of participants who had never developed PTSD plus those who had developed PTSD in the past but currently did not have PTSD (called lifetime PTSD) (N= 108). The PTSD group ($\overline{X}$ =40.17 years-SD=8.5) comprised those with delayed PTSD including those with chronic PTSD (N = 46). Based on this classification, there was no statically significant difference (F= .230, df=154, p=.632) between the PTSD ($\overline{X}$ =40.17 SD 8.5) and no-PTSD groups ($\overline{X}$ =42.5 years SD=9.04), with age as a covariate with cortisol level Table 3.

Table 2. PTSD and no PTSD groups

	Value	N
PTSD and	No-PTSD	108 (70%)
No- PTSD	PTSD	46 (30%)

Table. 3. PTSD and no-PTSD groups cortisol, covariate for age

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	26812.082(a)	2	13406.041	1.171	.313
Intercept	387177.938	1	387177.938	33.812	.000
Age	4447.421	1	4447.421	.388	.534
PTSD No PTSD	24264.738	1	24264.738	2.119	.148

a R Squared = .015 (Adjusted R Squared = .002)

11. A. 2. Gender:

The clear majority of the 156 participants were male (96.2%). The age distribution of the female participants (N =6) was between 36 and 42 years and narrower in range than the males. Although statistically non-significant, females had higher mean cortisol level than males table (8): 289.33 vs. 260 respectively, although this difference was not statistically significant and the number of females is small to compare it with males Table 4. Because of the small number of the participants in the sample gender was not taken as a variable for correlation.

Table. 4. Gender and Mean cortisol level (MCL)

Sex	Mean	N	Std. Deviation	df	M^2	F	Sig
Male	260.00	148	108.260				
Female	289.33	6	74.910	1	4961.295	.431	.513
Total	261.14	154	107.128				

11. B. PTSD and cortisol level:

11. B. 1. PTSD

There was no significant difference in the mean cortisol level between PTSD and no-PTSD groups: PTSD group mean level of cortisol ($\overline{X}$ = 112.51 nmol/l), and the no-PTSD group ($\overline{X}$ = 104.29 nmol/l) Table 5. Both of these figures are below 15th percentile for Kuwait population reference cortisol level: 160-1076 nmol/l. The participants with no PTSD symptoms (intrusions, avoidance or hyperarousal) they had mean level of cortisol ($\overline{X}$ =251.46 nmol/l).

Table. 5. T- test: PTSD and no-PTSD, and cortisol level (nmol/l)

Levene's Test for Equality of Variances				t-test for Equality of Means			
		F	Sig.	T	df	95% Confidence Interval of the Difference	
						Lower	Upper
Cortisol Level	Equal variances assumed	.914	.341	-1.40	152	-63.47	10.81
	Equal variances not assumed			-1.35	79.48	-64.91	12.25

11. B. 2. Cortisol levels

The timing of sleep was taken compared to sampling time. PTSD participants had a Mean of ($\overline{X}$ =4.28) hours (SD=2.8) hours of night sleep daily which significantly (p=.003, df=135, F=8.9) lower than participants without PTSD ($\overline{X}$ =5.65 hours SD=2.27). Both groups (PTSD and no-PTSD) had no significant difference (p=.821, F=.051) in the sampling time (duration between waking up from sleep and sampling time) it was ($\overline{X}$ =3.83 hours for PTSD) and ($\overline{X}$ =3.80 hours for no-PTSD). The sample was taken between 9-11 am for all the clients. When we correlated the sample time and cortisol level there was a negative correlation with statistical significance p.027. There was also a correlation between duration of sleep and cortisol level but it was not statistically significant (Table 6).

Table 6. Correlation between: sampling time, sleep duration and cortisol level (nmol/l)

		Sleep duration	Cortisol level
Sample timing	Pearson Correlation	-.478(**)	-.201(*)
	Sig. (2-tailed)	.000	.027
Sleep duration	Pearson Correlation		.161
	Sig. (2-tailed)		.063
Cortisol level	Pearson Correlation		
	Sig. (2-tailed)		

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

The range of cortisol levels for the total sample was 83-670 nmol/l (3 - 24.28 μg/dl) with mean of $\overline{X}$ = 261.14 nmol/l (9.46 μg/dl) and a SD = 107.128 nmol/l. This represents 7.7%-62.2% of the upper normal cortisol limit for the population in Kuwait. 74.5% of the participants had cortisol levels in the low normal level below 300 nmol/l Table 7.

Table. 7. Cortisol levels in the sample

Cortisol level nmol/l (μg/dl)	N	%
83-199 (3-7.21)	47	30.5
200-299(7.24-10.83)	68	44
300-399 (10.86-14.46)	23	15
>400 (14.49)	16	10.5
Total	154	100

Most of the participants had a cortisol level less than the 50th percentile 95.65 of participants with PTSD and 97.3% of those with no-PTSD diagnosis (Table 8).

Table. 8. Cortisol (nmol/l) Percentiles and PTSD

	PTSD	
	NO	YES
Cortisol ≤ 25th Percentile	N=72	N=25
	66%	54.8%
Cortisol ≥25th -50th Percentile	N=33	N=19
	31.3%	40.8%
Cortisol ≥50th Percentile	N=3	N=2
	2.7%	4.4%

Participants in relation to PTSD diagnosis (1st phase 1998 and 2nd phase 2003) were classified to: never PTSD, recovered PTSD, late onset PTSD and chronic PTSD. Comparison of four groups (using t-test of cortisol level and different PTSD categories) showed significant difference between delayed onset and chronic PTSD mean cortisol level (MCL) where the delayed group had lower MCL ($p<.05$) Table 9.

Table. 9. Cortisol level (nmol/l) and PTSD 1998 AND PTSD 2003

	N	Mean	SD	95% Confidence Interval		Min	Max
				Lower Bound	Upper Bound		
1 Never PTSD	57	256.39	107.927	227.75	285.03	101	605
2 Lifetime PTSD	28	261.86	111.613	218.58	305.14	83	670
3 Delayed PTSD	18	241.56	78.696	202.42	280.69	127	366
4 Chronic PTSD	19	294.67	125.266	232.37	356.96	139	551
PTSD (Delayed + Chronic)	46	279.61	112.5	-	-	127	568
No-PTSD (Never + Lifetime)	108	253.28	104.29	-	-	83	670

Independent Samples t-test: (Delayed onset and chronic PTSD): F=4.244, df=34, p.047

(Never PTSD and chronic PTSD) F=1.396, df=73, p=.241

11. C. Severity of Physical injury, PTSD and cortisol level:

There were no statistically significant differences between PTSD and no-PTSD participants, cortisol level and severity of injury as shown in Table 10. Severity of the trauma and cortisol level were not significantly correlated Table 11. Participants with trauma score up to 43 MCL ($\overline{X}$ = 232.86 nmol/l SD= 72.34) and those with injury score 106-230 MCL ($\overline{X}$ = 280.36 nmol/l SD=138.39) p= .031 df=42, F=4.974, but that was not associated with PTSD diagnosis Table 12.

Table. 10. Total injury score, cortisol level (nmol/l) and PTSD and No PTSD group

Source	df	F	Sig.
Corrected Model	72	.699	.833
Intercept	1	48.737	.000
Total injury score	1	.092	.767
Cortisol level	71	.708	.824

Table.11. Correlations between injury score and cortisol level (nmol/l)

		Cortisol Level
Total Injury Score	Pearson Correlation	-.032
	Sig. (2-tailed)	.769
	N	86

Table. 12. Cortisol level (nmol/l), injury score and PTSD

PTSD and Injury score	Mean	N	SD
Injury score <43 and no PTSD	236.12	17	73.439
Injury score <43 and PTSD	221.80	5	75.549
Injury score 44-104 and no PTSD	265.17	12	110.306
Injury score 44-104 and PTSD	236.78	9	83.237
Injury score 160-230 and no PTSD	271.12	17	136.219
Injury score 160-230 and PTSD	311.80	5	156.338
Injury score >230 and no PTSD	232.20	15	74.223
Injury score >230 and PTSD	275.00	6	105.628
Total	252.76	86	101.290

Independent Samples t-test (PTSD and no-PTSD) <43: df=20, F=.094, p=.763
(PTSD) <43 and 160-230: df=8, F=1.95, p=.199

11. D. Severity of PTSD symptoms, PTSD diagnosis, and cortisol level:

There were no significant differences between PTSD total symptoms severity (using CAPS) and cortisol level as shown in Table 13. Participants with mild symptoms (CAPS score ≤40) had $\overline{X}$ =251.89 SD=100.4 compared to participants with severe PTSD (CAPS Score ≥61) had $\overline{X}$ = 259.3 SD=102.8 p=.791 F=.071.

Table 13. Correlation Cortisol level (nmol/l) and severity of PTSD symptoms

		PTSD Symptoms
cortisol	Pearson Correlation	.025
	Sig. (2-tailed)	.760
	N	154

11. D. 1. Avoidance Symptoms:

The overall severity of the avoidance PTSD symptoms was not correlated with the levels of cortisol with PTSD diagnosis Table 14. The severity of the avoidance symptoms was divided based on the total score to severe avoidance score $\overline{X}$ > 12.5 and mild-moderate avoidance $\overline{X} \leq$ 12.5. We found that PTSD participants with severe avoidance had lower mean cortisol level ($\overline{X}$ =264 nmol/l) compared to those with mild-moderate avoidance ($\overline{X}$ =270.73nmol/l), but this was statistically not significant (F=.351, df 34, p=.558).

Table 14. Cortisol (nmol/l) and total Avoidance Score (CAPS) and PTSD and no PTSD.

Source	df	F	Sig.
Corrected Model	2	1.373	.257
Intercept	1	166.677	.000
Total Avoidance Score	1	.787	.376
PTSD No PTSD	1	.152	.697

11. D. 2. Arousal symptoms

The overall severity of the arousal PTSD symptoms was not correlated with the cortisol level, and PTSD diagnosis Table 15. The severity of the arousal symptoms were divided based on the total score compared to the ($\overline{X}$ = 12.7) to severe arousal $\overline{X}$ score > 12.7 and mild-moderate arousal $\overline{X} \leq 12.7$. We found that PTSD participants with severe arousal had lower mean cortisol level $\overline{X}$ =252.29 nmol/l compared to those with mild-moderate arousal $\overline{X}$ =299.75nmol/l, but this was statistically not significant (F=.351, df 34, p=.558)

Table 15. Cortisol (nmol/l), PTSD and no PTSD, and total arousal score (CAPS)

Source	df	F	Sig.
Corrected Model	2	1.322	.270
Intercept	1	180.525	.000
Total arousal score	1	.687	.408
PTSD No PTSD	1	2.487	.117

11. D. 3. Intrusive symptoms:

There was not a statistically significance in correlating participants with PTSD, no-PTSD, severity of intrusive symptoms and cortisol level Table 16. Table 17 shows correlation between the three main PTSD symptoms and cortisol level showing no significant correlation between these symptoms and cortisol level. The severity of the intrusive symptoms were divided based on the total score compared to the $\overline{X}$ = 8.4 to severe intrusion $\overline{X}$ score > 8.4 and mild-moderate intrusion $\overline{X} \leq$ 8.4. We found that PTSD participants with severe intrusion had lower mean cortisol level $\overline{X}$ =264 nmol/l) compared to those with mild-moderate intrusion $\overline{X}$ =302.86 nmol/l, but this was statistically not significant (F=1.6, df 34, p=.214)

Table 16. Cortisol (nmol/l), PTSD diagnosis, and total arousal score (CAPS)

Source	df	F	Sig.
Corrected Model	2	.994	.372
Intercept	1	243.30	.000
Total intrusive Symptoms	1	.040	.842
PTSD No PTSD	1	.867	.353

Table. 17. Correlation between Cortisol (nmol/l), PTSD Symptoms severity, Current avoidance, Current Arousal, and Current Intrusion

		PTSD Symptoms	Current avoidance	PTSD avoidance	Current Arousal	PTSD Arousal	Current Intrusion	PTSD intrusion	PTSD Severity
Cortisol	Pearson Correlation	.025	-.008	.030	-.045	-.037	.071	.141	-.077
	Sig. (2-tailed)	.760	.932	.776	.630	.728	.466	.203	.404
	N	154	117	90	117	90	108	83	120
PTSD Symptoms	Pearson Correlation		.099	.165	.181(*)	.232(*)	.061	.(a)	-.407(**)
	Sig. (2-tailed)		.286	.117	.048	.026	.524	.	.000
	N		119	92	119	92	110	85	122
Current avoidance	Pearson Correlation			.865(**)	.763(**)	.640(**)	.319(**)	.387(**)	-.307(**)
	Sig. (2-tailed)			.000	.000	.000	.001	.001	.003
	N			92	119	92	98	77	91
PTSD avoidance	Pearson Correlation				.833(**)	.819(**)	.498(**)	.576(**)	-.625(**)
	Sig. (2-tailed)				.000	.000	.000	.000	.000
	N				92	92	76	76	91
Current Arousal	Pearson Correlation					.804(**)	.435(**)	.533(**)	-.572(**)
	Sig. (2-tailed)					.000	.000	.000	.000
	N					92	98	77	91
PTSD Arousal	Pearson Correlation						.418(**)	.462(**)	-.586(**)
	Sig. (2-tailed)						.000	.000	.000
	N						76	76	91
Current Intrusion	Pearson Correlation							.909(**)	-.448(**)
	Sig. (2-tailed)							.000	.000
	N							85	83
PTSD intrusion	Pearson Correlation								-.588(**)
	Sig. (2-tailed)								.000
	N								83
PTSD Severity	Pearson Correlation								
	Sig. (2-tailed)								
	N								

* Correlation is significant at the 0.05 level (2-tailed). ** Correlation is significant at the 0.01 level (2-tailed).

a Cannot be computed because at least one of the variables is constant.

11. E. Psychiatric Co-morbidity, PTSD and Cortisol level:

11. E. 1. Somatic complaints and daily activities:

The problems related to general health and daily activities included (using CIDI): ability to perform usual activities, medium activities, low activities, perform less than wish to do, activities restricted due to physical health, activities restricted due to psychiatric problems, activities not done due to psychiatric problems, activities restricted due to pain, feeling calm and peaceful, feeling having great energy, feeling depressed and physical health interfered with social activities. Daily activities impairment were significantly correlated with PTSD diagnosis p<.05 Table 18, and highly correlated P<.001 with severity of PTSD symptoms, and cortisol level and was correlated with cortisol level p=.093 Tables 19 and 20.

Table. 18. ANOVA: PTSD diagnosis and deterioration in daily activities performance (CIDI)

				t-test for Equality of Means			
		F	Sig.	T	df	95% Confidence Interval	
						Lower	Upper
Daily Activities	Equal variances assumed	5.758	.018	-4.720	150	-8.315	-3.408
	Equal variances not assumed			-4.318	70.902	-8.568	-3.154

Table. 19. Correlations PTSD total symptoms, daily activities performance (CIDI) and cortisol level

		Daily Activities	Cortisol Level
PTSD Total score	Pearson Correlation	.476(**)	.095
	Sig. (2-tailed)	.000	.242
	N	152	154
Daily Activities	Pearson Correlation		.138
	Sig. (2-tailed)		.093
	N		150

** Correlation is significant at the 0.01 level (2-tailed).

Table. 20. Impairment in daily activity using CIDI and cortisol level (nmol/l)

	Daily Activities impairments	N	Mean	SD
Cortisol Level	Mild	61	263.52	83.184
	Severe	40	290.66	128.805

t-test: (mild and severe impairment): F=10.397, p=.002

11. E. 2. Physical symptoms

Physical symptoms were measured using the Gulf war Syndrome Questionnaire (GWQ), it consisted of 80 physical symptoms: e.g. headache, back pain, nausea, etc (see the Appendix Q20.1-Q20.80). Participants with PTSD had higher mean score of physical symptoms $\overline{X}$ =38.02, compared to no-PTSD participants with statistically significant difference p<.001 Table 21. Cortisol level was not correlated with PTSD diagnosis and severity of physical symptoms Table 22.

Table. 21. T-test Physical symptoms (GWQ) and PTSD diagnosis

				t-test for Equality of Means			
		F	Sig.	T	df	95% Confidence Interval	
						Lower	Upper
Physical Symptoms	Equal variances assumed	27.827	.000	-5.876	152	-29.84	-14.82
	Equal variances not assumed			-4.521	53.868	-32.24	-12.43

Table. 22. Correlation between: PTSD diagnosis, cortisol level, and physical symptoms (GWQ)

Source	df	F	Sig.
Corrected Model	59	1.727	.009
Intercept	1	132.211	.000
Cortisol	1	.865	.355
Physical Symptoms	58	1.716	.010

11. E. 3. Physical disorders:

Physical problems listed in GWQ (Q21.1-Q21.61) were correlated to PTSD diagnosis and cortisol level. The following disorders were analyzed. Table 20 showed that the following disorders were found more common in PTSD group with statistically significant difference: hypertension, G.I. problems, dysurea, joint pain, skin infections, hair and scalp disease, chronic fatigue, alcohol abuse and anxiety. None of these disorders correlated with severity of PTSD symptoms. Anxiety, GI problems, peptic ulcer and irritable bowel were correlated with levels of cortisol Table 23. With several independent tests, p value of .05 is inflated, so the Bonferroni correction procedure was used in each case. For the physical data there were 16 variables, so the corrected p value is .0032. Any test with a p value less than .003 is significant at the 5% level.

Table. 23. Physical disorders and PTSD and no-PTSD (Chi-Square), correlations (t-test) with severity of PTSD symptoms and levels of cortisol.

	No PTSD	**PTSD**	**Sig. Chi-Sq**	**Correlation with Cortisol t-test**	**Correlation with severity of PTSD symptoms CAPS t-test**
Hypertension	10 (9.2%)	10 (21.3%)	.038*	F=.486, p=.487	F=2.703, p=.102
Heart Disease	10 (9.2%)	6 912.8%)	.339	F=.918 ,p=.340	F=.776 ,p=.380
Bronchial Asthma	11 (10.1%)	3 (6.4%)	.342	F=.186 ,p=.667	F=.720 ,p=.397
Chronic Bronchitis	3 (2.8%)	4 (8.5%)	.123	F=.601 ,p=.439	F=.654 ,p=.420
Peptic Ulcer	14 (12.8%)	11 (23.4%)	.081	F=4.21 ,p=.042	F=2.26 ,p=.134
G.I. Problems	3 (2.8%)	6 (12.8%)	.022*	F=5.06 ,p=.026*	F=.143 ,p=.706
Irritable Bowel	15 (13.8%)	11 (23.4%)	.107	F=4.62 ,p=.033	F=.545 ,p=.462
Dysurea	2 (1.8%)	5 (10.6%)	.026*	F=.769 ,p=.382	F=.421 ,p=.517
Diabetes	22(20.2%)	9 (19.1%)	.535	F=.100 ,p=.753	F=.055 ,p=.815
Arthritis	8 (7.3%)	7 (14.9%)	.122	F=.439 ,p=.508	F=1.18 ,p=.277
Joint pain	10 (9.2%)	10 (21.3%)	.038*	F=.690 ,p=.408	F=1.10 ,p=.295
Skin infection	5 (4.6%)	7 (14.9%)	.034*	F=.907 ,p=.342	F=.119 ,p=.731
Hair scalp disease	(4.6%)	12 (25.5%)	.001*	F=.016 ,p=.900	F=2.26 ,p=.135
Chronic Fatigue	2 (1.8%)	6 (12.8%)	.010*	F=.324 ,p=.570	F=.157 ,p=.677
Alcohol Abuse	2 (1.8%)	5 (10.6%)	.026*	F=1.99 ,p=.160	F=.023 ,p=.878
Anxiety	11 (10.1%)	16 (34%)	.001*	F=15.5 ,p=.001*	F=.004 ,p=.951

10. E. 4. Generalized Anxiety Disorder (GAD) and anxiety symptoms

Clinical GAD was found only in five (10.6%) participants according to ICD-10 using CIDI questionnaire Table 24. All of the 5 participants with GAD (using ICD-10 CIDI) had PTSD. There was statistically significant difference p<.001 between PTSD and no-PTSD participants in the mean anxiety scores using SCL-90 Table 25. Participants with GAD had higher mean values of cortisol levels compared to no-GAD participants and it was statistically not significant using CIDI (probably due to small number), and the same was found using SCL-90R Tables 26. Participants with GAD showed no statistically significant difference with MCL, even in association with PTSD diagnosis Table 27.

Table. 24. GAD according to ICD-10, using CIDI and PTSD diagnosis.

		PTSD and No PTSD group		Chi-Square	
		NO PTSD	PTSD	df	Sig.
GAD	No GAD	109 100%	42 89.4%	1	.002
	GAD	0 .0%	5 10.6%		

Tale. 25. Total Anxiety Score and PTSD diagnosis.

	Mean	N	SD	df	F	Sig.
NO PTSD	47.2994	109	7.08964	1	31.594	.000
PTSD	56.2630	47	12.71172	154		

Table. 26. PTSD and No- PTSD group, cortisol level (nmol/l), and total score of anxiety symptoms SCL-90R

Source	df	F	Sig.
Corrected Model	28	3.093	.000
Intercept	1	214.142	.000
Cortisol	1	.363	.548
Total Anxiety SCL-90	27	3.108	.000

Table. 27. Cortisol level (nmol/l), PTSD and Anxiety

PTSDANX	Mean	N	SD
PTSD without Anxiety	259.81	21	94.178
PTSD and Anxiety symptoms	279.73	15	124.374
No PTSD and Anxiety symptoms	275.12	17	150.857
No PTSD and No Anxiety symptoms	256.31	101	99.343

t-test: (PTSD and No-PTSD) with anxiety df 30, F=.054, p =.818

(PTSD) with and without anxiety df= 34, F=2.57, p=.118

11. E. 5. Major Depressive Disorder (MDD) and depressive symptoms

Nine participants (5.8%) were diagnosed with MDD using ICD-10 criteria CIDI (7 had PTSD and 2 had no PTSD chi-Square p=.003), and 43 (27.6%) participants were identified as having depression using SCL-90R, 22 with PTSD i.e. 46.8% of PTSD participants had depression p<.001) Table 28. Participants with PTSD had higher mean total depression score using SCL-90R with statistically significant difference p<.001 Tale 29. Participants with PTSD with depression had significantly p<.001 higher mean depressive symptoms using SCL-90R ($\overline{X}$ =64.2) compared to no-PTSD participants with depressive symptoms ($\overline{X}$ =62.0).

Table 28. Prevalence of Depression among PTSD and no-PTSD group using SCL90R

		NO PTSD	PTSD	Total
SCL90R-	NO (0~1.75)	93	20	113
Depression		85.3%	42.6%	72.4%
	YES (1.76~4)	16	27	43
		14.7%	57.4%	27.6%
Total		109	47	156
		100.0%	100.0%	100.0%

Chi-Square: p<.001, df=1

Table. 29. PTSD and mean Total Depression score Score:SCL90R

	Mean	N	SD
NO PTSD	47.0667	109	7.41
PTSD	56.8028	47	11.83

Chi-Square F=38.70, df=1,156 p<.001

11. E. 6. Panic attacks

Only 9 (5.8%) of participants fulfilled ICD-10 criteria for panic attacks using CIDI. Most of these were participants with chronic PTSD, with statistically significant differences p=.022 Table 30. There were no statistically significant difference in the mean level of cortisol and presence of panic attacks Table 31. Participants with PTSD and panic attacks had lower but non-significant MCL compared with those without PTSD Table 32. Similarly, there was no correlation between cortisol level, PTSD and panic attacks Table 33.

Table 30. Panic attacks (CIDI scale) and PTSD and No PTSD groups

			Total
	NO PTSD	PTSD	
No Panic Attacks	106	41	147
	97.2%	87.2%	94.2%
Panic Attacks	3	6	9
	2.8%	12.8%	5.8%
Total	109	47	156
	100.0%	100.0%	100.0%

Chi-Square: p=.022 df=1

Table. 31. Panic attacks (ICD-10: CIDI) and mean cortisol level (nmol/l)

PANIC	Mean	N	SD	df	F	P
No Panic Attacks	261.77	145	105.346	1	.085	.771
Panic Attacks	251.00	9	140.011			
Total	261.14	154	107.128			

Table. 32. PTSD, Panic attacks (DSM-IV: CIDI) and mean cortisol level (nmol/l)

PTSD PANIC	Mean	N	SD
PTSD + Panic Attacks	193.00	5	59.578
PTSD + no Panic Attacks	280.23	31	108.085
No PTSD + Panic Attacks	323.50	4	186.888
No PTSD + no Panic Attacks	256.76	114	104.508

Independent Samples t-test (PTSD and no-PTSD and panic attacks df=34, F=1.57 p=.218

Table. 33. PTSD total symptoms, mean cortisol (nmol/l) and presence of panic attacks

Source	df	F	Sig.
Corrected Model	2	8.063	.000
Intercept	1	39.601	.000
Cortisol	1	1.732	.190
Panic	1	14.623	.000

11. E. 7. Alcohol and substance abuse

Sixteen percent of the participants were alcoholics, (29% of those with PTSD and 13% of those without PTSD p=.064), but there were no significant differences for this disorder and level of cortisol among PTSD participants Tables 34 and 35. Participants with alcohol abuse (N=26) had a lower MCL but statistically non-significant. The same lower MCL results were found when PTSD was associated with alcoholism compared to participants with PTSD without alcoholism. There were statistically significant correlations found between PTSD, cortisol and alcoholism p<.002 Table 36. Four participants were substance abusers, but there were no significant differences between the substance abuser, presence of PTSD and cortisol level, probably due to small number.

Table. 34. Alcoholism, mean cortisol level (nmol/l)

Alcoholism	Mean	N	SD	df	F	P
YES	233.90	26	99.290	1	2.037	.156
NO	266.68	128	108.177			
Total	261.14	154	107.128			

Table. 35. PTSD, Alcoholism and mean cortisol level (nmol/l)

	Mean	N	SD
PTSD without Alcohol	282.74	27	92.254
PTSD and Alcohol	232.00	11	125.630
No PTSD and Alcohol	235.29	15	79.537
No PTSD and No Alcohol	262.38	101	112.075

Independent Samples t-test (PTSD and no-PTSD with alcoholism): df=36, F=.535, p=.469

Table. 36. Univariate Correlation: PTSD, Alcoholism, mean cortisol level (nmol/l)

PTSD Total score

Source	df	F	Sig.
Corrected Model	2	5.570	.005
Intercept	1	30.282	.000
Cortisol	1	2.425	.122
HTO3	1	9.682	.002

a R Squared = .069 (Adjusted R Squared = .056)

11. E. 8. Cigarette Smoking and substance abuse

Nearly 50% of the participants were current smokers with statistically significant difference in PTSD group compared to no-PTSD participants p=.019 Table 37. Cigarette smoking (had higher levels of MCL) but was not found to be statistically related to level of cortisol and PTSD Table 38. Cigarette smokers who had PTSD had a lower but non-significant MCL compared with PTSD non-smokers ($\overline{X}$ =254.9, $\overline{X}$ =302.3 respectively p=.784) Table 39. There was no significant correlation between PTSD, cortisol level and presence of smoking history Table 40.

Table. 37. Smoking history and PTSD and No PTSD group

				Total
		NO PTSD	PTSD	
Smoking History	YES	46	29	75
		42.2%	61.7%	48.1%
	NO	63	18	81
		57.8%	38.3%	51.9%
Total		109	47	156
		100.0%	100.0%	100.0%

Chi-Square: p=.019, df=1

Table. 38. Cigarette smoking and mean cortisol level (nmol/l)

Smoking	Mean	N	SD	df	F	P
YES	263.75	75 (48.7%)	113.763	1	.086	.77
NO	258.67	79 (51.3%)	101.095			
Total	261.14	154	107.128			

Table. 39. PTSD, Cigarette smoking and mean cortisol level (nmol/l)

PTSDSMK	Mean	N	SD	df	F	P
PTSD without Smoking	302.30	10	112.841	3	.708	.548
PTSD and Smoking	254.96	26	103.275			
No PTSD and Smoking	267.38	50	118.717			
No PTSD and No Smoking	252.87	68	99.215			

Independent Samples t-test: (PTSD smokers and non-smokers p=.784, F=.077, df=34

Table. 40. Univariate correlation: cortisol (nmol/l), PTSD and cigarette smoking history.

Cortisol Level

Source	Type III Sum of Squares	df	F	Sig.
Corrected Model	22377.144(a)	2	.975	.380
Intercept	1080901.565	1	94.154	.000
Smoking	12.483	1	.001	.974
PTSD and No-PTSD	21386.411	1	1.863	.174

a R Squared = .013 (Adjusted R Squared = .000)

11. E. 9. Other psychiatric co-morbidities

Global Severity Index (GSI) of SCL-90R scale has been reported significantly more prevalent among PTSD participants Table 41. However, in this study, this index was not significantly related to cortisol level in the PTSD and no PTSD groups Table 42.

Table. 41. Global Severity Index (GSI) and positive symptom distress index (PSDI) of SCL-90R with PTSD

PTSD and No PTSD group		Total Score:SCL90R-Global Severity Index GSI
NO PTSD	Mean	47.1497
	N	109
	SD	7.30527
PTSD	Mean	56.6102
	N	47
	SD	12.15583

ANOVA: GSI df=(1,154), F=36.036, p<.001.

Table. 42. Cortisol (nmol/l), PTSD and no PTSD to Total scores of Global severity index and positive symptoms distress index SCL-90R.

Source	df	F	Sig.
Corrected Model	4	1.569	.186
Intercept	1	29.158	.000
GSI	1	2.547	.113
PTSD No PTSD	1	1.046	.308

a R Squared = .041 (Adjusted R Squared = .015)

11. E. 9. A. Somatization,

There were no statistically significant differences between PTSD and no-PTSD groups, cortisol level and degree of somatization Table 43. Participants with moderate to severe somatization symptoms (N=16) according to SCL-90 had lower MCL, but those with PTSD diagnosis had a higher level of the MCL Tables 44.

Table. 43. Cortisol (nmol/l), PTSD and no PTSD to total scores of somatization (SCL-90)

Source	df	F	Sig.
Corrected Model	2	1.049	.353
Intercept	1	322.215	.000
Somatization	1	.147	.702
PTSD No PTSD	1	1.368	.244

a R Squared = .014 (Adjusted R Squared = .001)

Table. 44. PTSD, Somatization and mean cortisol level MCL(nmol/l)

PTSD Somatization	Mean	N	SD
PTSD with no Somatization	258.36	25	97.575
PTSD with Somatization	290.27	11	126.944
No PTSD with no Somatization	262.76	113	107.545
No PTSD with Somatization	174.40	5	76.484
Total	261.14	154	107.128

t-test: (PTSD with and without somatization) F=(34) 1.228 p=.276

11. E. 9. B. Obsessive Compulsive Disorder OCD

Only 4 participants fulfilled criteria for OCD using CIDI questionnaire. There was statistically significant difference for having OCD and level of cortisol Table 45, but this is a small number for doing correlations. This significant difference was not found with OCD symptoms according to SCL-90 (N=16) although these participants had higher MCL Table 46. Those with PTSD and comorbid obsessive compulsive disorder OCD had higher MCL than those with OCD but without PTSD ($\overline{X}$ =428.75 vs. $\overline{X}$ =256.67) but it was statistically not significant Table 47. No significant correlation between PTSD, cortisol, and total OCD symptoms SCL-90R Table 48.

Table. 45. Obsessive compulsive disorder OCD according to CIDI , and mean cortisol level (nmol/l)

OCD	Mean	N	SD	df	F	P
No OCD	256.67	150	103.018	1	10.689	.001
OCD	428.75	4	140.514			
Total	261.14	154	107.128			

Table. 46. Obsessive compulsive symptoms according to SCL-90, and mean cortisol level (nmol/l)

OCD	Mean	N	SD	df	F	P
No OCD symptoms	256.50	138	103.414	1	2.52	.115
OCD symptoms	301.19	16	132.190			
Total	261.14	154	107.128			

Independent Samples t-test: df=152, F=1.924, p.167

Table. 47. Mean cortisol level (nmol/l), PTSD and no PTSD to Total scores of Obsessive compulsive symptoms OCD (SCL-90R)

PTSDOCD	Mean	N	SD
PTSD with no OCD	252.92	24	91.857
PTSD with OCD	309.60	10	130.143
No PTSD with no OCD	257.51	112	105.837
No PTSD with OCD	276.13	8	140.220

ANOVA: (PTSD with and without OCD): F2.033, df=32, p.164

Table. 48. Cortisol (nmol/l), PTSD and no-PTSD to total scores of Obsessive compulsive symptoms OCD (SCL-90)

Source	df	F	Sig.
Corrected Model	2	2.207	.114
Intercept	1	269.892	.000
OCD	1	2.434	.121
PTSD No PTSD	1	.389	.534

a R Squared = .028 (Adjusted R Squared = .016)

11. F. Life events, PTSD and cortisol level:

The results of life events scale, (using the cut-off point of >300 points as significant evidence of stress experience), we found that there was statistically significant difference between PTSD and no-PTSD groups in the mean score of life events p<.001 Table 49. But there was no statistically significant difference between PTSD and no-PTSD, cortisol level and total life events score Table 50 and 51.

Table. 49. PTSD and Life Events Scale mean Score

PTSD and No PTSD group	Mean	N	Std. Deviation	F	df	Sig.
NO PTSD	222.70	109	149.00	24.10	1	.001
PTSD	361.61	47	189.45			

Table. 50. Cortisol, PTSD and no PTSD to Total scores of life events scale

Source	df	F	Sig.
Corrected Model	2	.974	.380
Intercept	1	213.737	.000
Total Life Events Scale	1	.000	.985
PTSD No PTSD	1	1.716	.192

Table. 51.Cortisol level in PTSD and no-PTSD with LES score > and < 300 points

PTSD and Life Events Scale	Mean	N	SD
No PTSD and LES score <300	250.00	61	99.954
No PTSD and LES score >300	279.01	24	127.734
PTSD and LES score <300	275.93	14	130.275
PTSD and LES score >300	263.14	22	91.390

t-test: (No PTSD with <300 and >300 LES): F=.804 df=83, p=.373

(>300 LES PTSD and no PTSD) F=.557, df=44, p=.460

(PTSD >300 and <300 LES) F=1.36, df=34, p=.252

11. G. Family history of psychiatric disorder, PTSD and cortisol level:

Past family history of psychiatric illness was reported by 25.4% of the participants. This positive family history of psychiatric disorders was correlated with lower MCL, but it was statistically not significant Table 52. Those with PTSD had statistically no significant difference compared to those without psychiatric family history with cortisol level Table 53.

Table. 52. Family history of psychiatric disorders, and mean cortisol level MCL (nmol/l)

Family Psychiatric	Mean	N	SD	df	F	P
YES	249.17	40	98.000	1	.673	.413
NO	265.34	114	110.253			
Total	261.14	154	107.128			

Table. 53. PTSD, Family history of psychiatric disorders, and mean cortisol level MCL (nmol/l)

PTSD Family history	Mean	N	SD	df	F	P
PTSD with no Family Psych. History	267.68	22	115.722	3	.515	.672
PTSD with Family Psych. History	271.15	13	97.968			
No PTSD with no Family Psych. History	265.08	91	110.125			
No PTSD with Family Psych. History	238.57	28	96.241			

12. Discussion:

12. A. PTSD and cortisol level:

Low normal morning serum cortisol was found in this study; 64.3% of the participants were below the 25th percentile (physically injured with and with no PTSD), and 93% were below 50% percentile of Kuwaiti population. This means that our control group which is physically injured with no PTSD were also having low cortisol levels indicating the possible role of injury in cortisol level as discussed below section 10-I. Studies (e.g. Yehuda et al, 1996) of neurobiology of PTSD suggest that there is a lower baseline cortisol level in patients with PTSD, other non-PTSD people under chronic stress, and even patients under chronic medical diseases. None of the participants had high normal levels of cortisol (i.e. >860nmol/l). The mean cortisol of participants with delayed onset PTSD was lower than that of participants with chronic PTSD with statistical significance $p<.05$, but the MCL of the PTSD group was not significantly different from those who had never had PTSD or had had lifetime PTSD. This is supporting our hypothesis that patients with chronic PTSD have low cortisol levels, which are compared to those with delayed onset PTSD or lifetime PTSD. Both sets of cortisol means were low: the mean cortisol for participants with PTSD $\overline{X}$ =279.61 nmol/l and the mean cortisol for participants without PTSD 253.28 nmol/l. Participants with chronic and delayed onset PTSD has significant statistical difference in MCL ($\overline{X}$ =294.67 nmol/l and $\overline{X}$ =241.56 nmol/l respectively) $p<0.05$. Yehuda (1993-b, 1995-b, 1996, and 2001) has reported in several studies that patients with PTSD have low cortisol levels, but this response is not what is known about normal stress reaction in which elevation of cortisol is the normal response. Low level cortisol levels have been reported in different populations, e.g., in the Gulf War veterans (Kellner et al, 1997), Vietnam veterans (Yehuda 1990, 1993-b), World War II Holocaust survivors (Yehuda et al, 1995-b), and rape victims (Resnick et al, 1995). However, Bonne et al (2003) observed that normal cortisol level continue to be present in chronic PTSD. This was observed in 8 PTSD out of 21 trauma survivors in whom cortisol levels was taken at 1st week and at 6 months. Cortisol levels at 1 week did not predict subsequent PTSD in Bonne et al study and the survivors with and without PTSD had similar mean levels of cortisol at both time points. Cortisol levels at 6 months negatively correlated with self-reported PTSD symptoms within PTSD participants. In our study we found similar results that war-injured survivors with and without PTSD had similar MCL 13 years after the trauma.

There were also no significant differences between different subgroups of our sample in relation to normal low levels of cortisol (defined as the lower 25th percentiles of cortisol level), in PTSD and no-PTSD groups 54.8% and 66% respectively. All our sample participants were had varying degree of severe war injury. Victims had the injury during the 7 months invasion and occupation period; hence any one of them was prone to develop PTSD anytime in their life time as shown from follow up of this sample during the period of 1998-2003 as shown that recovered, chronic and delayed onset PTSD persistently were having low normal levels of cortisol levels as all they have sustained trauma and had or have a PTSD diagnosis. Still some 47.2% of the participants never developed PTSD. Among these participants 11 (19%) had no PTSD symptoms, but the rest (81%) had varying degree of PTSD symptoms with mean PTSD symptoms using CAPS in 1998 and 2003 were $\overline{X}$ =12.6 and $\overline{X}$ =15.9 indicating that they had sub-syndromal type of PTSD not fulfilling DSM-IV criteria according to CAPS. This is supported by Yehuda et al (1998-a) study that when low levels of cortisol appear in trauma survivors they will be at risk of developing PTSD compared to others with normal levels. In our study we do not have a control group that had not sustained a serious traumatic event; however the norms of morning cortisol in Kuwait 28-1076 nmol/l, Ministry of Health report (1997), and our results were consistently lower than these norms. We did not find significant differences between delayed onset and recovered PTSD in relation to cortisol levels, but there was significant difference between delayed onset and chronic PTSD, lower MCL in delayed onset compared to chronic PTSD. Young et al (2004) in a study of salivary cortisol level in traumatized women with delayed and lifetime PTSD or without PTSD compared to controls found normal levels without significant differences between the groups. They concluded that neither recent nor past PTSD affected saliva cortisol in the sample of women. In our hypothesis that patients who completely recover from PTSD may have normalized their cortisol levels whereas patients with partial recovery, cortisol levels changes may persist, we found in our results that patients who had not recovered completely from PTSD and still had few PTSD symptoms did not had normal cortisol level. This could be explained by the findings of Yehuda (2006) that observed cortisol effects are due to the first impact on the HPA axis which may also explain our findings of low cortisol in individuals who never diagnosed with PTSD and had low cortisol level.

Another study of Gulf war veterans Golier et al, (2002) found normal cortisol levels in PTSD veterans. 17 Gulf War Veterans (GWV) with PTSD, 12 GWV without PTSD, and 22 non-deployed, non-military, healthy participants have been studied. They found that Gulf War veterans with PTSD did not differ significantly from those without PTSD on basal cortisol level, but had lower post-dexamethasone cortisol levels and significantly higher percent of cortisol suppression. They have reached the conclusion that the number of glucocorticoid receptors per lymphocyte did not differ between veterans with and without PTSD. In an epidemiological 10 year follow-up study of PTSD patients, Young et al (2004) found that trauma per se did not lead to sustained increases in either cortisol or catecholamine levels, and PTSD was associated with increased catecholamine levels, not, however, with increased or decreased cortisol levels. There was no distinct pattern in cortisol levels between past and current PTSD; but it was higher in women with lifetime major depressive disorder and comorbid PTSD, compared with women with neither disorder or with either disorder alone and a significantly higher mean cortisol level in men with lifetime major depressive disorder alone, compared with men with neither disorder or with both disorders. Young et al (2004) found that persons with PTSD did not show lower urinary cortisol levels than persons with no history of trauma or persons with history of trauma but not of PTSD. Moreover they did not have lower urinary cortisol levels compared to persons with a history of major depressive disorder or persons with neither disorder. Our findings supported our hypothesis that patients with severe trauma would have low cortisol levels, and the presence of co-morbid psychiatric and /or physical disorders may affect cortisol level. In our follow-up study, however, we found that 13 years after the trauma our participants had low cortisol levels regardless of PTSD diagnosis. Lipschitz et al (2003) in a study of adolescents with PTSD measuring cortisol level before and after dexamethasone suppression test showed no differences between participants with current PTSD and those traumatized without PTSD or control participants. This could be explained by the severity of the traumatic injury and the physical disability as a consequence of the injury which will affect the HPA axis at the period following the trauma having lower levels of cortisol making the patient vulnerable to PTSD at any time in his life span. The roles of other factors on cortisol level are discussed below.

In our study we found that both participants with PTSD and without PTSD have lower cortisol levels than the general population. This raises the question as to whether this is a specific effect of PTSD or it is the significant trauma and stress exposure that is the main factor. Reviewing 22 studies from the recent literature we calculated the effect size using Cohen's d and r factors as shown in Table 54. There were no consistent findings as the results were variable due different methodologies. Comparing the effect size among participants who did not develop PTSD after trauma and those who were not traumatized and were used as controls the following studies: de Kloet CS et al, (2007), Lipschitz DS et al, (2003), and Yehuda R (2004-b), found effect size using Cohen's d of (–0.620), (-0.818) and (–0.883) respectively. In these studies the differences in the cortisol level was clear showing the effect of the stress of the trauma rather than due to the development of PTSD disorder. The weighted mean effect size for these studies is -0.73. This difference supports that trauma itself rather than PTSD has an impact on HPA axis. The weighted mean effect size for studies of the cortisol level between trauma PTSD and no trauma no PTSD was -0.973. This is more supporting. The weighted mean effect size was calculated by adding (Cohen's d effect size X sample size) for each study, then adding these and dividing the total of these studies by the total number of all sample sizes of these studies.

Table 54. Effect size using Cohen's d and r values of 22 published studies and the current study of cortisol level between trauma (PTSD and no PTSD) and no trauma controls.

References	Trauma: PTSD		No Trauma	Effect Size		p
	Yes	No		Cohen's d	r	
Yehuda R. (2007-a)*	(13)638.4± 217.5	(17) 851.9±428	-	-0.628	-0.29	<.0001
Otte C. (2007)	(17)15.6±5.6	-	(16)14.2±6.3	0.234	0.116	0.65
Yehuda R, (2007-b)*	(17)40.1±5.4	(16)59.2±6	-	-3.346	-0.858	<0.05
Baker DG. (2005)	(8)78.2±66.4	-	(8)67.02±27.1	0.22	0.109	NS
Yehuda R. (2002-c)*	(28)9.91±2.84	(22)11.4±3.75	-	-0.447	-0.218	-
Liberzon I. (1999-b)*	(17)12.1±3.9	(14)9.3±2.9	(11)7.9±2.4	0.814 **0.525	0.377 0.254	-
Baker DG. (1999)*	(11)84.4±55.3	-	(12)76.2±19.7	0.197	0.098	-
Yehuda R. 91996)*	(15)7.45±1.69	-	(15)9.06±1.92	-0.890	-0.406	0.02
de Kloet CS. (2007)	a.m.(23)11.6±5.5	(22)12.5±6	(24)16.1±5.6	-0.156 **-0.620	-0.077 -0.296	0.2
	p.m.(23)3.9±3.3	(22)3.9±1.7	(24)4.4±2.7	0 -0.221	0 -0.11	0.75
Lipschitz DS. (2003)	(20)664±352	(9)339±111	(19)561±367	1.245 **-0.818	0.528 -0.378	0.06
Golier JA. (2006)*	(12)14.42±2.88	(14)12.9±3.5	(12)11.9±2.9	0.474 **0.311	0.230 0.153	-
Bierer LM (2006)	(32)46.3±20	(14)72.2±22.4	-	-1.219	-0.52	-
Griffin MG (2005)	(25)6.6±2.6	(8)17.7±8.3	(14)15.2±4.3	-1.804 **0.378	-0.669 0.185	-
Otte C (2005)*	(20)52±15	(16)43±23	-	0.463	0.225	0.19
* Yehuda R (2004-b)	(26)12.5±4.7	(8)9.3±3.2	(10)12.5±4	0.795 **-0.883	0.369 -0.404	-
Yehuda R (2004-a)	(17)12±4.7	(9)13.6±3.2	-	-0.397	-0.195	-
Neylan TC (2002)	(11)886±312	-	(11)987±428	-0.269	-0.133	0.46
Olff M (2006-b)	(39)284.9±89.3	-	(44)397.5±149.6	-0.9212	-0.418	<0.001
Randall D M (2002)	(7)7.3±2.49	-	(13)9.85±2.36	-1.05	-0.465	0.43
Otte C (2002)	(10)1325±159	-	(10)1269.4±144.8	0.365	0.179	-
Kellner M (2004)	(15)372.7±318	-	(20)398.6±314.7	-0.081	-0.04	-
Roth G (2006)	(17)40.1±5.4	(16)59.2±6	-	-3.34	-0.058	0.051
Current study: PTSD vs. No PTSD D-PTSD vs. No PTSD	(46)279.6±112.5 (18)241.5±78.6	(108)253.2±104.2 (57)256.3±107.9	-	0.243 -0.156	0.120 -0.078	

* Combat, ( ) is sample size, Mean ±SD , D-PTSD : delayed onset PTSD

** No PTSD with and without trauma

12. B. Total injury score, PTSD and cortisol level:

Our results showed that there was no significant relationship between severity of injury and low levels of cortisol regardless of PTSD status. This may simply be a consequence of the presence or absence of any injury, rather than there being any numeric correlation or relationship with the magnitude of the injury, i.e. injury by itself may be sufficient to provoke a similar change in the HPA axis, independent of injury severity. Regression analysis also indicated that severity of PTSD symptoms and severity of the physical injury were not related to cortisol level for the participants in this study. We also found a negative correlation between severity of the injury and MCL. The hypothesis that the degree of disability may not have an effect on cortisol level was supported as we found that the injury was sufficient to affect the cortisol level and not the duration or severity. Regression analysis or participants with high normal cortisol levels showed no relationship for severity of the PTSD symptoms and injury severity. Schechter et al (2004) found studied a sample of 41 mothers of young children (ages 8-50 months) with childhood sever traumas with PTSD. Maternal salivary cortisol levels taken before and 30 minutes after a videotaped play paradigm with their children, involving two separations and reunions; and cortisol reactivity 30 minutes after separation stress. They found significant negative correlation between baseline cortisol and: trauma severity, delayed PTSD symptoms and dissociative symptoms, and atypical maternal behavior. This supports our findings; although in our study was 13 years after the trauma. The differences in relation to PTSD could be explained by the acute stimulus in Schechter study the participants were subjected to, and the nature of PTSD disorder current compared to chronic and delayed onset in our sample. Furthermore in our sample the physical disability due the injury is there as a reminder which affected the whole participants.

11. C. Age, PTSD and cortisol level:

We found lower levels of MCL in participants above 60 years compared to participants below 40 years $\overline{X}$ =241.75 nmol/l and $\overline{X}$ =259.18 nmol/l respectively but it was statistically not significant. Yehuda et al (2005-a) found low normal cortisol level in older participants with PTSD. This was based on a study of 23 Holocaust survivors with PTSD, 19 Holocaust survivors without PTSD, and 25 participants who had not been exposed to the Holocaust of WW-II. This supported our findings of low cortisol level in this age group. But we could not found any significant correlations between PTSD, age and cortisol level in our sample. This could be due to

presence of other factors in association with PTSD that could affect cortisol levels in PTSD and no PTSD group.

12. D. Somatic and psychological problems in PTSD and cortisol level

In the present study, participants with PTSD showed significantly worse somatic and psychological problems than participants without PTSD; cortisol level was also correlated with severity of daily activity impairment. These participants reported poorer health, more work problems, poorer, psychological health, and lower level of energy. Physical symptoms (e.g. chest pain, headache, palpitation, bouts of irritability, breathing problems, bronchial asthma, sleeping difficulties, hyper vigilance) were also significantly correlated $p<.001$ with PTSD, but not with cortisol level. PTSD participants were significantly having hypertension, gastrointestinal problems, joint pain, skin infection, hair and scalp disorders, chronic fatigue, alcohol abuse, and anxiety. Impairment in daily activities, the presence of multiple physical symptoms and the prevalence of physical disorders in PTSD participants compared to participants with no-PTSD could have an impact on the level of cortisol. Chronic fatigue is associated with dysfunction of the HPA axis with low cortisol level. This link was based on the observed associations between physical or psychological stress and illness onset, the co-morbidity with major depression and the predominance of fatigue in disorders of the HPA axis such as Addison's disease, Roberts (2004). While Gaab et al (2002) studying 21 subjects with CFS failed to find any significant difference in morning response in patients and controls. In our sample 8 (6 with PTSD and 2 had no-PTSD) participants were having chronic fatigue symptoms (using GWQ) but there was no statistical significance p.570 in cortisol level between those with and without chronic fatigue symptoms. McLean et al (2005) proposed PTSD and chronic fatigue after trauma could interact after tissue damage through a model of central neurobiological systems as discussed below.

12. E. Major Depressive disorder, PTSD and cortisol level

High levels of cortisol in persons with major depression have been reported in other studies (e.g. Yehuda et al (1990). In our study, 46.8% of PTSD participants had depressive symptoms above cutoff point for depression using SCL-90R. Participants with depression had non-significantly higher cortisol levels ($\overline{X}$ =272.01 nmol/l) compared to participants without depression ($\overline{X}$ =256.94 nmol/l) p=.230. Moreover the severity of depressive symptoms (using SCL90R)

comparing participants with PTSD ($\overline{X}$ =64.2) and those without PTSD ($\overline{X}$ =62) were statistically significant p<.001. Participants with PTSD and depressive symptoms ($\overline{X}$ =282.27) had higher MCL compared to participants with no-PTSD and depressive symptoms ($\overline{X}$ =224.54 nmol/l) but it was not significant (p=.063). Our results are consistent with the literature in reporting hyperactivity of the HPA axis in patients with depression, but demonstrated that co-morbidity with PTSD can affect HPA function in these patients i.e. lower cortisol because of the effect of PTSD. This supports our hypothesis that co-morbid psychiatric disorders with PTSD may have an impact on cortisol levels

Oquendo et al (2003) also showed that patients with PTSD in combination with depression had lower level of cortisol than those with only depression. This study was based on sample of 58 patients with MDD and PTSD and only MDD. Lipschitz (2003) found different results, that there is an enhanced cortisol level was found in patients with co-morbid depression associated with PTSD which is consistent with our findings. McFarlane et al (1997) showed that cortisol levels, measured shortly after road traffic accidents, were lower in survivors who subsequently developed PTSD than in those who developed depression. Our study confirmed the findings in the literature of low cortisol in patients with PTSD, but when PTSD is co-morbid with depression the effect of higher cortisol with depression will raise the cortisol level in these patients. Only 19 (17 had no-PTSD and 2 had PTSD) participants (12.3%) had no depressive symptoms, the remaining sample had depressive symptoms. Halbreich et al, (1989) found normal Dexamethasone Suppression Test response and plasma cortisol in MDD and PTSD, in contrast with evidence of higher plasma cortisol in those with MDD alone. In our study the effect PTSD and depression together was obvious on the level of cortisol. Yehuda et al (1990) found lower 24-h urinary cortisol subjects with PTSD compared with controls, regardless of whether they had co-morbid depression.

Yehuda et al (2004-a) studied the association between MDD and PTSD in 52 patients and 10 controls found that cortisol hypersuppression in PTSD appears not to be dependent on the presence of traumatic events prior to the focal trauma, but it may affect cortisol suppression in MDD. In this study we showed that participants with major depressive disorder and co-morbid PTSD had higher plasma cortisol levels compared to participants with PTSD and without depression but still in the lower mean levels of cortisol of the general population.

12. F. PTSD subtypes, cortisol level

In this study, we found significant differences on mean cortisol levels between chronic and delayed onset PTSD ($\overline{X}$ =294.67 nmol/l and $\overline{X}$ =241.56 nmol/l respectively) p<.05. Bremner 2003 studied 41 participants: 23 with PTSD and 18 healthy controls. Salivary cortisol levels were measured before and after a stressful cognitive challenge. They found that PTSD group had 61% higher cortisol levels in the time period leading up to the cognitive challenge, and 46% higher cortisol levels during the time period of the cognitive challenge, compared to controls. Both PTSD patients and controls had a similar 66-68% increase in cortisol levels from their own baseline with the cognitive challenge. Following the cognitive challenge, cortisol levels fell in both groups and were similar in PTSD and control groups. PTSD patients appeared to have an increased cortisol response in anticipation of a cognitive challenge relative to controls. Although cortisol has been found to be low at baseline, there does not appear to be impaired in cortisol response to stressors in PTSD. Our findings are supported by the literature that low cortisol is found in patients with delayed onset PTSD, but we found that when PTSD is chronic (in our sample over 5 years since diagnosis the level although it is in the lower normal range for the population it is higher than the delayed onset. The participants who recovered from the PTSD and those who were having severe trauma and never had PTSD yet had lower levels of cortisol.

12. G. Life events, PTSD and cortisol level

Participants with a high number of life events in the past twelve months on the day of their assessment showed a score of ≥300 in cortisol levels. In participants with PTSD there were lower levels of cortisol ($\overline{X}$ =263.14 nmol/l) compared to participants with PTSD and scores <300 ($\overline{X}$ =275.93) but it was not significant p=.252. In participants without PTSD diagnosis and LES score of >300 had higher cortisol levels ($\overline{X}$ =279.01 nmol/l) compared to those with LES <300 ($\overline{X}$ = 250 nmol/l) without significant difference between the two groups. This showed the effect of life events as a continuous stressor on participants with PTSD and cortisol level. The vastness of the literature in this issue has precluded a through examination of this issue. To highlight the importance of life events Solomon (1990) examined the relationships of life events, locus of control, social support and the severity of PTSD following breakdown in combat in 255 Israeli soldiers who suffered a combat stress reaction episode during the 1982 Lebanon War and were followed 1 and 2 years after their participation in combat. They found that there are significant

relationships between PTSD 1 year after war, on the one hand, and life events, locus of control, and social support reported 1 year later, on the other. They found that life events, locus of control and social support were found to be cross-sectionally associated with the severity of PTSD 2 years after the war, but the relationship was not significant once prior PTSD status was controlled for. They also found that social support measures were the only variables that significantly contributed to PTSD after their redundancy with the other variables and their relations with prior PTSD were controlled for. They concluded that life events influenced PTSD indirectly through their impact on social support.

Clancy et al (2006) examined whether trauma exposure before, during, and/or after military service contributed to current levels of PTSD and adjustment in a retrospective study, of 422 male veterans diagnosed with PTSD. They found that nonmilitary-related trauma was prevalent in this sample (90%) and regression analyses for PTSD symptom severity revealed that age, greater combat exposure, and a history of physical assault after military service, childhood physical abuse, adult sexual trauma, and a history of being physically assaulted during military service were significantly associated with PTSD symptom severity. They have suggested that several variables, including age, greater combat exposure, and premilitary and postmilitary traumas, are associated with increased PTSD symptomatology.

12. H. Severity of PTSD symptoms and cortisol level

Spivak et al (1997) observed that low cortisol levels in patients with PTSD were responsible for the maintenance of the symptoms of PTSD patients. In our study participants with severe intrusive, arousal and avoidance symptoms had lower mean cortisol levels compared to those with mild-moderate symptoms but it was statistically not significant using t-test. Participants with low normal cortisol levels and chronic PTSD had higher rates of intrusion and arousal symptoms and these were significantly different than those with delayed onset PTSD or those without PTSD. High avoidance symptoms were more frequent in participants with delayed onset PTSD compared with those chronic PTSD and those without PTSD. Furthermore, we found that participants without PTSD at time of assessment displayed intrusive and avoidance symptoms and to a lesser extent arousal symptoms which we think a sub-syndromal of PTSD.

Participants who recovered from PTSD continued to have the same low normal levels of cortisol compared with those who have delayed onset PTSD and those with chronic PTSD. These findings are supported by those reported in Spivak et al (1997). Otte et al (2002) concluded that despite considerable arousal and anxiety, cortisol level did not increase during the first exposure and the 20th re-exposure of repeated imaginary events. The cortisol level in these participants was low throughout the study. The continuation of symptoms observed in our study affecting cortisol levels in participants without PTSD indicated that sub-clinical symptoms may persist in those but who are exposed to traumatic events. Aardal-Eriksson (2001) measured morning and evening salivary cortisol in 31 United Nations soldiers: 5days, 2 months and 9 months following mine accident in Lebanon. They found that sub-clinical PTSD symptoms (using IES) were associated with low salivary cortisol soon after the event. Goenjian et al (1996) reported an 88% suppression of cortisol at 8 a.m. in adolescents with greater severity of PTSD symptoms after exposure to a natural disaster (an earthquake) compared to 87% suppression of cortisol at 8 a.m. in adolescents with fewer PTSD symptoms. They concluded that in patients with chronic PTSD, persistent intrusion symptoms may constitute continued episodes of distress and evoke repeated physiological stress responses, which, over time, alter HPA axis function. These findings suggest that there may be diurnal changes associated with severity of posttraumatic stress symptoms.

12. I. General comments about the results:

The low levels of cortisol in PTSD patients are a deviation of the normal physiological response to stress:

1. The lack of differences among subjects with various types of PTSD in our studied population may be associated with the presence of physical injuries in all subjects as it was reported in the introduction that physical injury can cause changes in cortisol levels. Hence this difference may be an effect of the injury combined with the trauma. To review the etiology of PTSD, whiplash-associated disorders (WAD), and fibromyalgia, after motor vehicle collision (MVC), McLean et al (2005) proposed a model of central neurobiological systems: physiologic and neuroanatomical structures involved in the stress response, and the development of all 3 disorders. There is evidence suggesting a role for stress response systems in the development of these disorders is presented. The proposed model is that the development of chronic symptoms incorporates the potential for interactions between past experiences, acute stress responses to trauma, post-MVC behavior, and cognitive/psychosocial consequences to alter activity within brain regions which

process pain and to result in persistent pain, as well as psychological sequelae, after MVC. It was concluded that new models are needed to stimulate deeper examination of the interacting influences of initial tissue damage, acute pain, psychosocial contingencies, and central stress pathways during chronic symptom development after MVC. They suggested that dysregulation within central stress response systems may play a critical role in the development of PTSD after the trauma which may leads e.g. to "over consolidation of memories". The central neurobiological processes after the trauma involve: interaction between direct effect of tissue injury and the emotional responses to the experienced threat, and the interaction of acute stress after the trauma is shaped by genetics and prior trauma experience.

2. Past personal and family psychiatric history in our study showed no statistically significant difference in relation to cortisol levels. 96.6% of the participants denied that they had past psychiatric history (prior to the trauma as self report using the general questionnaire) and 25.4% had a family history of psychiatric problems. Yehuda et al (1998-b) gave one possible explanation for low cortisol levels. They attributed the increased vigilance, and sensitization to trauma in PTSD patients, to prior traumatic experiences, or genetic factors. This will cause a decrease input to the hypothalamus from cortical and sub-cortical regions, which will lead to a decrease a baseline cortisol level. Yehuda et al (2000-a) measured 24-hour urinary cortisol levels in 35 adult children of Holocaust survivors and 15 comparison individuals. They found that cortisol levels were low in participants with PTSD and in those who had a parent with PTSD, but where higher in individuals who had neither. The low cortisol levels in Yehuda et al (2000) study were associated with parental PTSD rather than the parent's exposure to trauma during the Holocaust. They attributed the low cortisol levels with the risk of developing PTSD. Unlike our findings, they also found that participants exposed to trauma without developing PTSD did not necessarily have low cortisol levels. Yehuda et al (2000-a) concluded that exposure to trauma alone cannot be associated with lower cortisol levels. In our prospective study in which we reassessed our cohort sample, after six years from the first assessment, we found that out of 86 participants who did not develop PTSD in 1998, 28 (32.5%) developed PTSD in 2003. We did not have cortisol levels for the participants in 1998, but at the reassessment 44 of 57 (77%) participants who never had PTSD had cortisol levels less than 300 nmol/l. This indicates that the traumatic event of PTSD is one of the main factors that will lower cortisol level in patients who at time of investigation has PTSD and in whom that they may develop PTSD sometime in their life since their HPA axis has been disturbed. This finding is also supported by Mason et al (1986) and Marshall et at (2002) who showed that cortisol level start low, and remain low for many

years after the trauma and diagnosis of PTSD. Anisman et al (2001) explained that the results of some of the studies that show increased levels of cortisol in patients with PTSD could be attributed to pervious trauma and parental psychiatric disorders. There may be other factors that could explain why in spite of low cortisol in the majority of the sample the timing of PTSD presentation as in DSM-IV is different.

3. In our sample the cortisol level was measured 13 years after the trauma and it showed low values. We do not have blood samples from the immediate time following the trauma or even the first clinical assessment of the subkects. Yehuda et al (2005-b) emphasized the importance of genetic and environmental factors that may predispose an individual to PTSD. It appears that type of trauma may not be relevant to developing PTSD, in that specific biological factors, as indicated by cortisol level, may predispose one to developing PTSD. Resnick et al (1995) found low cortisol in rape victims in the immediate aftermath of the trauma if they had had a previous traumatic experience. Similar findings were reported by Aardal-Eriksson et al (2001) in groups of veterans with pre-service low cortisol level who showed a higher PTSD symptomatology than others with normal levels. Yehuda et al (2005-b) have concluded that mothers who developed PTSD after September 11th terrorist attack had low cortisol levels. In addition, one-year-old children of these mothers with PTSD also had low cortisol levels, which indicated the relevance of in utero contributors to putative biological risk for PTSD. This was not observed in mothers without PTSD or their children. Goldney et al (2000) in study of motor vehicle accident victims have reported that observed that low cortisol levels immediately after the accident were associated with the development of PTSD and high cortisol levels were associated with the development of depression.

4. In our sample the interview process was likely to have been fairly provocative for these individuals as indicated by the reported degree of distress and hence the failure of the cortisol to rise may be a pertinent issue. This was also found in individuals with trauma who did not developed PTSD. Aerni et. al. (2004) studied the reasons why in PTSD patients the body does not increase cortisol level to prevent traumatic memory retrieval, i.e. why there is a failure of the (shut off) protective mechanism to inhibit retrieval of such memories which predispose to chronicity in PTSD. In other words, that the failure in HPA axis to increase cortisol level in these individuals allows for the memories of the traumatic event to remain as high cortisol levels in acute stress inhibit memory retrieval in healthy human participants. Aerni et al (2004) gave 10

mg/day of hydrocortisone daily for 1 month to 3 patients with PTSD. They found that low-dose cortisol treatment reduces the cardinal symptoms of PTSD, and there is a 38% reduction in the daily rated symptoms of traumatic memories. In this study cortisol administration was seen to reduce PTSD symptoms by altering cortisol feedback regulation. In another study, patients in ICU taking steroids had a reduced risk for developing PTSD later on life Schelling et al (2001).

5. Charney et al (1999) have found normative or slightly elevated levels of cortisol in panic patients. Marshall et al (2002) conducted a pilot study to compare noradrenergic functioning and HPA axis functioning in PTSD, panic disorder, and normal control subjects, assessing both baseline levels and response to clonidine challenge. They found that PTSD patients had lower cortisol, compared to patients with panic disorder. They conclude that PTSD and panic disorder are on the opposite sides of the spectrum with respect to baseline cortisol. In our study participants with panic attacks without PTSD had higher MCL compared to participants with panic attacks with PTSD but it wasn't statistically significant.

In our sample, participants with OCD assessed using CIDI had significantly ($p<.001$) higher MCL compared to participants with no OCD. This was also observed in participants with PTSD and co morbid OCD although it was statistically not significant. Monteleone et al (1997) studied the cortisol level in 20 drug-free obsessive-compulsive patients (10 males and 10 females) and 20 age- and sex-matched healthy subjects. They found that the baseline plasma cortisol secretion was significantly increased in patients with OCD compared to the controls healthy subjects. They concluded that there is hyperactivity in the hypothalamic-pituitary-adrenal axis in obsessive-compulsive patients.

In our sample, participants with GAD had higher MCL than participants with no GAD with statistical significance ($p=.019$). When PTSD is co-morbid with GAD the MCL was lower than those with GAD and without PTSD although it was statistically not significant. But participants with PTSD with GAD were having higher MCL than participants with PTSD and without GAD. The high co-morbid psychiatric disorders, such as major and minor depression, phobia, and panic disorders, have been reported by Castanon et al (2002) who hypothesized that these disorders influence HPA axis functioning and hence lead to lower cortisol level.

Alcoholism is a common co-morbid disorder in patients with PTSD and it is associated with HPA axis abnormalities Adinoff et al (2005) and Gianoulakis et al (2003). Alcoholism was found in 16.8% of the total sample, and 29% of participants with PTSD and 13% of those without PTSD. Among participants with and without alcohol abuse, and with and without PTSD, MCL was found to be lower in the group with alcoholism but without statistical significance. Alcohol abuse in our sample were not associated with PTSD cortisol level when these co-morbidity is associated together which is consistent with what Brady (2006). They investigated the HPA axis reactivity to the cold presser task (CPT) among 119 individuals with alcohol dependence, PTSD, and co-morbid alcohol dependence and PTSD. Thy found that the HPA response in the co-morbid alcohol-PTSD group was not significantly different than that of the alcohol-only or PTSD-only groups

In our sample the nicotine effect was observed more in injures without PTSD i.e. in trauma survivors that did not develop PTSD yet. This role was also examined in the literature. Lipschitz et al (2003) indicated that nicotine may increases plasma cortisol levels in patients with PTSD, Yehuda (2006) gave explanation for the variability in cortisol measurements that nicotine can contribute to the stability of the results.

6. Our results of having low cortisol values in war physically traumatized individuals with and with no PTSD raise the following challenges about the following factors explaining the low cortisol findings in trauma survivors with PTSD.

A. Yehuda et al (1999) attributed the low levels of cortisol due to immune changes in patients with PTSD which may explain the associated physical disorders and the altered cortisol receptors sensitivity and the low levels of cortisol. If that is the case this could not explain why in our study, we found those participants who were traumatized and never diagnosed having PTSD had low cortisol levels (mean 251.46 nmol/l) below the 27^{th} percentile of the general population. Moreover participants with no PTSD with varying degrees of intrusion, avoidance, and arousal symptoms of PTSD symptoms (a sub-syndromal of PTSD) had also low cortisol levels. This could indicate that PTSD is a syndrome with its development being different from one individual to another based on multiple factors as discussed below, the role of HPA axis will depend on other factors that facilitate it in highly predisposed individuals and the manifest it early while others although they have the changes (low cortisol) but symptoms fail to be manifested at early stages of the syndrome. Yehuda et al (2002-c) explanation that the low

cortisol levels with sustained norepinephrine will boost the memory of the traumatic event, encoded it, and sustains the distress by high level of arousal, and if cortisol fails to adequately shut down adrenaline, leading to low cortisol level and sustained symptoms of PTSD.

B. Yehuda el al (2002-d) pproposed that low Cortisol levels in patients with PTSD could be due to maladaptive learning pathway to fear response, i.e. there is a sensitive HPA-axis which may explains the hyperactivity and hyper-responsiveness in PTSD.

C. Southwick et al (2003) have hypothesized that the cortisol activity turns off the HPA axis through negative feedback to the sensitive receptors in the brain. In our sample we do not have previous cortisol samples at the immediate time after the trauma, but the low cortisol levels in the participants with chronic PTSD may indicate that this turn off could be persistent, even though participants who recovered from PTSD had the same low cortisol levels which is another support and could indicate a chronicity of this disorder.

D. Kanter et al (2001) thought that it could be due to a sub-clinical adrenocortical insufficiency. They tried to explain the low cortisol levels and enhanced hypersuppression by using the Metyrapone stimulation test. In this test Metyrapone was given to prevent steroid genesis from the adrenal, and participants were given cortisol during the test to enhance more the suppression. They found that there was no greater suppression of ACTH (as it would be expected), there was no difference with controls. This supports the low cortisol levels in patents with PTSD.

E. Castanon et al (2002) assumed that low Cortisol level in patients with PTSD is due to the circadian rhythm of cortisol with varying cortisol levels over the course of 24 hours. It is possible that if we sampled cortisol at more frequent intervals during 24 hours, we might have found significant differences in cortisol levels between PTSD participants and no-PTSD participants.

F. Marshall et al (2002) proposed that there could be different forms of PTSD i.e. heterogeneity within PTSD depending on the level of cortisol. In our study we found an association between PTSD type and cortisol level. Among the 18 participants with delayed PTSD 14 had cortisol level of <300 nmol/l. In the 18 participants with chronic PTSD 11 with cortisol levels <300 nmol/l and 7 had varying levels of cortisol up to less than 600 nmol/l. This

could be due to other “not yet known” contributory factor(s) that may play role in this anxiety disorder affecting the HPA axis in different way giving the picture of multiple forms for one disorder.

G. Marshall et al (2002) have hypothesized that the observation of low normal levels of cortisol in PTSD participants is related to the methodological problem with the studies. Such methodological problems as not taking into account differences in participants' circadian rhythms or times of awakening, sample size or sample selection, not always controlling for smoking, drinking, medication use, amount of physical activity, and other factors like the incidence of depression, or gender related factors might explain the inconsistency in the findings.

H. Different diagnostic approach in different studies. Young et at (2004) raised another possibility that the diagnostic assessments in most studies were based on results from structured diagnostic interview and not a clinical diagnosis. The tool we have used for PTSD diagnosis is CAPS, and when we used DSM-III and compared it with DSM-IV criteria we did not found any significant difference. Delayed PTSD was found in 48 (30.8%) according to DSM-III, and 49 (31.4%) according to DSM-IV.

I. Kanter et al (2001) hypothesized that low normal levels of cortisol among participants with PTSD may be due to increased levels of corticosteroids-binding globulin (CBG) that could mask the level of cortisol since CBG protein binds with most of the available cortisol and thus the measured low cortisol level is the free non-bound cortisol.

J. Oquendo et al (2003) found that age differences in participants with PTSD could explain the differences in cortisol levels. They found that older patients had high cortisol levels. In our sample, we did not found such statistical difference. We found that participants with PTSD older than 50 years had low normal levels of cortisol as did younger age groups.

K. Lipschitz et al (2003) discussed other factors that may contribute to cortisol level. These factors included: nicotine use which may increases plasma cortisol levels; different cortisol measures in different studies i.e. plasma total or salivary free cortisol, oral contraceptives, use of psychotropic medications, and physical activity levels of participants all have different effects on cortisol measures. In our sample 59 (45%) of the sample are nicotine smokers. The

MCL was higher among PTSD 25(69%), than non-PTSD 34 (40%). In spite of that smoking showed no statistical significant difference affecting cortisol level in PTSD participants.

L. The effect of Interleukin IL-1ß on cortisol level was investigated by Interleukin IL-1ß enhances CRF, which in turn increases ACTH and cortisol production in normal participants. It is possible that desensitization of the HPA axis in chronic PTSD patients counteracts the stimulator effect of IL-1ß on cortisol secretion. As a compensatory mechanism IL-1ß will increase in PTSD to overcome the enhanced negative feedback of the HPA axis and cortisol suppression in PTSD. The high levels of IL-1ß can be explained by an already suppressed HPA axis which is not capable of inhibiting IL-1ß (Sweep et al, 1991, Spivak et al (1997), Yehuda et al (2000-b), Baker et al (2001), Castanon et al (2002), and Anthony et al (2005).

Bachumann et al (2005) and Anthony et al (2005) have proposed that the two common glucocorticoid receptors polymorphisms: N363S and BclI appear to contribute to the population variance in glucocorticoid receptors sensitivity, and there is some evidence that there may be a genetic predisposition to PTSD. Bachumann et al (2005) examined 118 Vietnam war veterans with PTSD and 42 combat exposed Vietnam\ war veterans without PTSD, for glucocorticoid receptors sensitivity (both N363S and BclI), and dexamethasone suppression test and the dermal vasoconstrictor assay. The DST and GR polymorphisms were also performed in 42 combat exposed Vietnam War veterans without PTSD. They found that the plasma cortisol levels were not significantly different in PTSD and controls and the same for dexamethasone suppression test. The cortisol suppression in PTSD patients did not correlate with Clinician Administered PTSD Scores (CAPS). It was concluded that the N363S and *Bcl*I GR polymorphisms were not more frequent in PTSD patients than controls and reported population frequencies

N. Another explanation for low Cortisol in patients with PTSD that this due to desensitization in chronic stress at which the effectiveness of cortisol is inhibited. Axelrod et al (1984).

O. The finding that both the PTSD and non PTSD have lower cortisol than the general population raises the questions as to whether this is a specific effect of PTSD or significant stress exposure.

13. Conclusions:

The following Table 55 summarizes the results:

Table 55. Summary of the findings: PTSD and no-PTSD groups and psychosocial variables

	Variable		PTSD	No-PTSD
	1 (M+SD)	2 (M+SD)	M+SD	M+SD
Age 1. PTSD 2. No-PTSD	40.17+8.5	40.17+8.5		
Sleep duration (hours)*			4.28+2.8	4.28+2.8
1.Delayed and 2.chronic PTSD *	241.5+78.6	241.5+78.6		
1. Injury score ≤43, 2. score 106-230*	232.8+72.3	232.8+72.3		
1.Mild PTSD ≤40, 2.Severe ≥61	251.89+100.4	259.3+102.8	-	-
1. Avoidance <12.5, 2. Severe >12.5	270.73	264	-	-
1. Arousal <12.7, 2. Severe >12.7	299.75	252.29	-	-
1. Intrusion <8.4, 2. Severe >8.4	302.86	264	-	-
1. Severe ADLs impairment*, 2. Mild	290.6+128.8	263.5+83.5	275.8+117.5	305.4+140.5
1. Severe physical symptoms, 2. Mild	206+74.36	275.6+112.4	316+114.5	268.17+111
1. Moderate psychoticism*, 2. No	280.8+94.5	260.3+107.8	265.7+109.6	311.1+131.7
1. Severe Neuroticism, 2. Mild	286.8+119.1	262+102.7	264.9+96.8	266.6+143
1. Severe Extraversion*, 2. Mild	237+83.2	305+126.8	248.4+88.4	230.1+67.9
1. High Pulse rate, 2. Normal Pulse	274+98.2	254.3+111.3	297.1+115.7	270.8+94.5
1. Systolic BP, 2. Normal BP	304.1+140.9	242.3+112.9	317.4+123.2	335.2+164.5
1. High BMI, 2. Normal BMI	226.9+119.7	261+118.1	253.5+94.6	274.1+114.9
1. High WHR, 2. Normal WHR	260.6+102	263.2+129.3	267.4+106.6	259.1+102.8
1. LES score >300 2. LES score <300	270.8+110.7	255.7+105.2	263.14+91.3	279+127.7
1.GAD 2. No GAD	277.28+136.6	256.9+98.1	279.7+124.3	259.8+94.1
1. MDD 2. No MDD	272.01+113	256.9+104.9	282.2+108.7	224.5+67.6
1.Panic attacks No Panic attacks	251+140	261.7+105.3	193+59.5	280.2+108
1. Alcohol Use 2. No Alcohol Use	233.9+99.2	266.6+108	232+125.6	235.2+79.5
1. Cigarette 2 No Cigarette	263.7+113.7	258.6+101	254.9+103.2	267.3+118.7
1. Somatization 2. No Somatization	254+124	261.9+105.4	290.2+126.9	174.4+76.4
1. OCD* 2. No OCD	428.75+140.5	256.6+103	309.6+130.1	276.1+140.2
1. Hostility 2. No Hostility	287.5+110.4	258.7+106.8	307+132.2	256.4+63.2
1. Family Psychiatric History FPH 2.No	249.1+98	265.3+110.2	271.1+97.9	238.5+96.2

* $p<.05$, M = mean, SD = Standard Deviation

1. There were lower baseline cortisol levels in participants with PTSD. War survivors who sustained physical injury have low normal cortisol levels. The mean cortisol of participants with PTSD (delayed and chronic), and participants without PTSD (never PTSD and recovered from PTSD) has no statistically significant difference between them. There was a statistical significant difference between those with delayed onset PTSD and chronic PTSD, MCL lower in delayed onset PTSD.

2. Follow up of war injured survivors for 6 years as in our sample; these survivors were prone to develop PTSD at any time since the war or to have chronic PTSD.

3. Trauma itself rather than PTSD may have an impact on HPA axis.

4. The following factors were high MCL: Severe ADLs impairment* Moderate psychoticism (EPQ) *, Severe Neuroticism (EPQ), LES score >300, GAD, MDD, Cigarette, OCD*, and Hostility.
* $p<.05$

5. Participants with PTSD had higher MCL in association with the following factors: Severe physical symptoms, Severe Extraversion (EPQ)*, High Pulse rate, High WHR, GAD, MDD, Somatization, OCD*, Hostility, Family Psychiatric History

6. Our results showed that participants with low levels of cortisol ($\leq 25^{th}$ percentile) with or without PTSD had no statistical significant difference in relation to total injury score. We found significant difference in MCL in participants with and high trauma score regardless of PTSD diagnosis.

7. In this study, age was not associated to cortisol level. There were no significant differences between younger and older participants in relation to the level of cortisol in relation to PTSD diagnosis.

8. There was significant difference between PTSD types in relation to cortisol level delayed onset had significantly lower MCL compared to chronic PTSD.

9. Both MDD and dysthymia did have enhancing effect on the level of cortisol in participants with PTSD.

10. A significant increase in the number of negative life events was found in participants with PTSD compared with participants with no-PTSD.

11. Low levels of cortisol in patients with PTSD were responsible for the continuation of the symptoms of PTSD patients.

12. Family psychiatric history in our study was associated with higher MCL.

13. In our study 91.7% of the participants had low normal MCL. Low cortisol at the time of the trauma could contribute to the future development of PTSD, and to the future development of PTSD.

14. OCD (as comorbid disorder in participants with PTSD) was associated with higher levels of cortisol compared with PTSD patients without OCD.

Chapter VI. Chronic PTSD and Thyroid Functions

1. Introduction:

The first association between traumatic stress and thyroid function abnormalities was described as early as in 1825, Mason et al (1994). The Hypothalamic pituitary thyroid (HPA) axis involves the release of thyrotropin-releasing hormone (TRH), from the hypothalamus, which stimulates the secretion of thyrotropin stimulating hormone (TSH) from the anterior pituitary gland. TSH in turn, stimulates the thyroid gland to secrete thyroxine (T4) and triiodothyronine (T3). All T4 comes from the thyroid gland and only about 20% of T3 from the thyroid gland. The remaining 80% of T3 comes from deionization of T4 by other body tissues, including brain. Although there is always much more T4 than T3 in serum, the ratio between them is important because T3 is more potent and faster acting. Apparently each tissue makes T3 according to its need; T4 is chiefly a prohormone Prange et al (1999). Prange proposed two general mechanisms that may shift the balance between T3 and T4. First the thyroid gland may change its pattern of secretion; second other tissues may change their rates of deionization. There are two pieces of evidence for this: first the thyroid hormones have negative feedback effects on TSH secretion, and probably on TRH secretion, whether these properties can be followed in disease conditions is unknown. Second when TRH is given chronically, the dynamics of the HPA axis are such that the system adapts and values tend to return to baseline. Under conditions of severe and sustained stress, the sympathetic nervous system can command the thyroid gland or other elements of the thyroid axis to respond as if to an emergency.

Endocrine changes in response to stress depend on various factors, in particular the duration and the type of stressor, Bauer et al (1994). The results of studies on stress-induced changes in hormones of the HPT axis are contradictory as TSH levels seem to rise in acute stress and fall in chronic stress, Bauer et al (1994). There are differences among studies between the severity and chronicity of PTSD symptoms, and severity of co-morbid depression between groups stress hormones. Smith et al (1989) reported that serum cortisol was found to be low, normal or even high, adrenocorticotropic hormone (ACTH) to be low among veterans with chronic PTSD. Other stress hormones related to stress responses are thyroid stimulating hormone (TSH) and growth hormone (GH), Smith et al (1989). In the standard (TRH) stimulation test, an exaggerated TSH response has been reported in PTSD patients in contrast to the blunted TSH response observed in depression, Newport et al (2000). In acute stress, reduction of both total and free T4 and of total and free T3 was observed, as well as there were increases in TSH Morgani et al (2000).

Olff et al (2006) examined the levels of six HPA and HPT-axis in 39 civilians with chronic PTSD and 44 healthy volunteers. Her results showed that PTSD individuals had significantly lower plasma cortisol, prolactin and TSH levels compared to the control group. The difference between TSH levels in patients and comparison subjects only emerged after controlling for relevant background variables. Haviland et al. (2006) studied 22 adolescent girls with PTSD due to sexual abuse shortly after the trauma, they found a significant relationship free and total T3 that is correlated negatively with PTSD: the average free T4, total T4, free T3, total T3, and TSH levels were within age-specific laboratory reference range limits, as were most individual concentrations. The strongest correlations ($p < .05$) were between free T3 and PTSD total score (−.50), PTSD—avoidance/numbing (−.49), and general distress (−.48); and between total T3 and depression (−.46), general distress (−.45), and PTSD—arousal (−.44). Other studies reported a positive relation i.e. elevated T3 levels with PTSD combat veterans Wang et al (1999) and was also found by civilian trauma of sexually abused women Friedman et al (2005). Wang et al (2006) argued that different adaptive survival strategies in the civilian and combat environments could explain the discrepancy of these results, and there could be stages in responding to overwhelming stress in PTSD in which thyroid hormones are first suppressed and then become elevated.

In this study we evaluated the thyroid function in a sample of war injured survivors with and without PTSD. The thyroid function examined included free T3, (fT3), free T4 (fT4), and TSH. The effect of psychiatric co-morbid disorder on the thyroid function in survivors with PTSD was studied. The blood samples in this study were drawn 12-13 years after the original (war) trauma, hence three subtypes of PTSD were studied in relation to thyroid function alternations: recurrent (chronic), delayed, and recovered type. Many of the analyses used are categorical rather than continuous statistical methods.

2. Hypotheses:

The following hypotheses were tested.

Thyroid functions: free thyroxin (fT4), free triiodothyronine (fT3), and thyroid stimulating hormone (TSH) in patients with PTSD: The hypotheses are:

1- Patients with PTSD have different HPT axis activity throughout the course of this disorder.

2- Patients with chronic PTSD have stable thyroid activity compared to those with acute PTSD.

3- Patients who recovered from PTSD have normal thyroid functions regardless of the hyperarousal, avoidance or intrusive PTSD symptoms remaining after the recovery phase.

4- Co- morbid psychiatric disorders associated with PTSD had minor effect on HPT axis in patients with chronic PTSD.

5- Degree of disability, age, and duration of PTSD symptoms could have an effect on the HPT axis.

The following parameters will be tested: fT3, fT4 and TSH. The following groups of participants in association with PTSD: Delayed onset PTSD, chronic PTSD, recovered (lifetime) PTSD, and participants without PTSD diagnosis.

3. Results

3. A. PTSD and thyroid function:

The following classification was done based on the normal range of thyroid functions based on Kuwait norms:

(1): fT3 (LN) Low Normal ≤ 3.6pmol/l (2.33 pg/ml), Normal (N) 3.61~4.89pmol/l (2.34-3.17pg/ml), High Normal > 4.89 pmol/l (3.17pg/ml)

(2): fT4: Low Normal (LN) ≤13.12pmol/l (168.85ng/dl), Normal (N) 13.12~19.34pmol/l (168.85-248.9 ng/dl), High Normal (HN) >19.34pmol/l (>248.91ng/dl

(3): TSH: Low Normal (LN) (≤0.74), Normal (N) (0.741~2.20), High Normal (HN) (2.201~5)

The primary clinical difference within the tested cohort sample was in PTSD diagnosis. The sample included 123 war injured survivors that were tested in 1998 and were retested for the second time in 2003. Comparing the results of 1998 and 2003 in relation to PTSD diagnosis, it was found that, 31 participant (19.9%) fulfilled DSM-IV criteria for delayed PTSD (i.e., previously not diagnosed as having PTSD in 1998), 17 (10.9%) had chronic PTSD (diagnosed at both times as having PTSD), 21 (13.5%) recovered from PTSD (lifetime – were diagnosed in 1998 and not in 2003), and 87 (55.8%) never diagnosed as having PTSD since the trauma in 1990-1991. These four groups were compared for the thyroid hormone differences, PTSD symptom severity as measured by the CAPS, presence of co-morbid disorders in association with PTSD diagnosis, severity of the traumatic event, and other associated symptoms of PTSD. The four groups also differed were compared for the association of physical problems and personality traits.

The mean level of fT4 was 15.59 pmol/l with (SD = 2.621) Table 1. Only 5.1% (*N*=8) had high normal levels of fT4 19.34pmol/l and up to 26 pmol/l. The rest of the participants: 14.1% (N=22) were having low Normal fT4 levels ≤ 13.12pmol/l (168.85ng/dl) and 79.5% (N=124) were having normal fT4 levels 13.12~19.34 pmol/l (168.85-248.9 ng/dl).

The mean level of fT3 was 5 pmol/l with (SD=3.5 pmol/l). Fifty nine percent of the sample had high normal levels of fT3.

The mean TSH level was 1.33 IU/l (SD = 0.9610). Most of our participants (66.7%) had a normal levels of TSH 0.741~2.20IU/l, whereas 22.4% had low TSH levels ≤0.74 IU/l, and only 9.6% (N=15) had high normal levels ≥2.201 IU/l with max recorded level of 8.8 IU/l.

Table. 1. fT3 Pmol/l (pg/ml), fT4 pmol/l (ng/dl), TSH in the studied sample

	fT3			fT4			TSH		
Mean	5.001 (3.247)			15.596 (200.720)			1.330		
SD	.5946 (.3861)			2.6215 (33.738)			.9610		
Min.	3.5 (2.27)			9.5 (122.265)			.0		
Max.	6.5 (4.22)			26.0 (334.62)			8.8		
Level	LN	N	HN	LN	N	HN	LN	N	HN
N	0	63	91	22	124	8	35	104	15
%	0	40.4	59.1	14.1	79.5	5.1	22.4	66.7	9.6

fT3 (LN) Low Normal ≤ 3.6pmol/l (2.33 pg/ml), Normal (N) 3.61~4.89pmol/l (2.34- 3.17pg/ml), High Normal > 4.89 pmol/l (3.17pg/ml) **fT4**: Low Normal (LN) ≤13.12pmol/l (168.85ng/dl), Normal (N) 13.12~19.34pmol/l (168.85-248.9 ng/dl), High Normal (HN) >19.34pmol/l (>248.91ng/dl). **TSH**: Low Normal (LN) (≤0.74), Normal (N) (0.741~2.20), High Normal (HN) (2.201~5)

3. A. 1. Age

Those who were less than 40 years showed higher but non-significant values of fT4, and TSH as compared to the groups older than 60 years of age; and similarly fT3 was lowest value with high age groups above 60 years Table 2. Free T3 was significantly different for PTSD and non-PTSD subjects. For all other age groups Table 3 participants with PTSD had no significant mean differences in fT4 or TSH values compared to non-PTSD participants of the same age group. In an ANOVA, Age and PTSD diagnosis interact in predicting fT4, indicating that age moderates the effect of PTSD on fT4 Table 4.

Table 2. fT3, fT4, TSH and age categories

Age groups		fT3 level	fT4 level	TSH level	FT3/FT4
≤40 years	Mean	5.076	15.850	1.324	.324718
71	SD	.5405	2.2478	1.1169	.045267
41-50 years	Mean	4.918	15.478	1.291	.326531
60	SD	.5747	3.0374	.8657	.062091
51-60 years	Mean	5.173	15.100	1.613	.350760
15	SD	.7759	2.4986	.6312	.070972
>60 years	Mean	4.638	15.150	1.150	.310700
8	SD	.6989	2.8127	.6141	.043078
df		3	3	3	3
F		1.967	.514	.557	1.207
Sig.		.163	.673	.644	.309

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

Tables. 3. PTSD (According to DSM-IV) Age and mean: fT3, fT4, TSH, and fT3/fT4

PTSD and age categories		fT3 level	fT4 level	TSH level	FT3/FT4
No PTSD and age <40 years	Mean	5.104	16.035	1.332	.322518
N=50	SD	.5314	2.1542	1.2659	.045882
PTSD and age <40 years	Mean	5.010	15.410	1.305	.329957
N=21	SD	.5691	2.4546	.6629	.0444208
No PTSD and age 41-50 years	Mean	4.942	15.421	1.285	.330733
N=48	SD	.5701	3.2117	.9313	.0667690
PTSD and age 41-50 years	Mean	4.825	15.708	1.317	.309723
N=12	SD	.6092	2.3106	.5589	.0352914
No PTSD and age 51-60 years	Mean	5.315	14.623	1.623	.368931
N=13	SD	.6986	2.3138	.6660	.0558454
PTSD and age 51-60 years	Mean	4.250	18.200	1.550	.232650
N=2	SD	.7778	.9899	.4950	.0300520
No PTSD and age >60 years	Mean	4.800	15.957	1.157	.302457
N=7	SD	.5686	1.7747	.6630	.0391270
PTSD and age >60 years	Mean	3.500	9.500	1.100	.368400
N=1	SD	.	.	.	.

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

Table. 4. PTSD (According to DSM-IV) Age and mean: fT3, fT4, TSH, fT3/fT4

Univariate analysis

fT3

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	4.635(a)	7	.662	1.954	.065
Intercept	1076.469	1	1076.469	3177.28	.000
PTSD_No_PTSD	1.731	1	1.731	5.109	.025
Age	1.960	3	.653	1.929	.128
PTSD_No_PTSD * Age	1.621	3	.540	1.595	.193

a R Squared = .086 (Adjusted R Squared = .042)

fT4

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	74.628(a)	7	10.661	1.593	.142
Intercept	11027.314	1	11027.314	1648.12	.000
PTSD_No_PTSD	.591	1	.591	.088	.767
Age	19.068	3	6.356	.950	.418
PTSD_No_PTSD * Age	63.124	3	21.041	3.145	.027

a R Squared = .071 (Adjusted R Squared = .026)

TSH

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	2.490(a)	7	.356	.374	.916
Intercept	76.611	1	76.611	80.573	.000
PTSD_No_PTSD	.591	1	.591	.621	.432
Age	1.305	3	.435	.458	.712
PTSD_No_PTSD * Age	.735	3	.245	.258	.856

a R Squared = .018 (Adjusted R Squared = -.029)

3. A. 2. Gender, PTSD and thyroid function:

There were 6 females who participated in the study. Only 2 of them had DSM-IV criteria of PTSD. Table 5 shows that females with PTSD had higher but non-significant score mean of PTSD symptoms severity ($\overline{X}$ = 84.5) compared to males with PTSD ($\overline{X}$ = 66.97). Females showed lower mean levels of fT3, TSH, fT3/fT4 and higher mean levels of fT4, all within the range Table 6. Due to the small number of female in the sample further analysis will not be of clinical significance.

Table. 5. Gender and PTSD severity

SEXPTSD	Mean	N	SD
Male PTSD	66.9714	35	18.72791
Male no PTSD	22.8783	115	18.96078
Female PTSD	84.5000	2	30.40559
Female no PTSD	31.0000	4	20.99206
Total	33.7692	156	26.94770

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

T-test: (PTSD: males and females) F=.695, df=35, p.410

Table 6. Gender and thyroid function: fT3, fT4, TSH, and fT3/fT4.

SEX OF THE PERSON		fT3 Level	fT4 Level	TSH Level	FT3/FT4
MALE	Mean	5.002	15.576	1.338	.327706
148	SD	.5972	2.6038	.9700	.055669
FEMALE	Mean	4.983	16.083	1.138	.315563
6	SD	.5776	3.2671	.7438	.042348
Total	Mean	5.001	15.596	1.330	.327233
154	SD	.5946	2.6215	.9610	.055152
df		1	1	1	1
F		.006	.215	.248	.278
Sig.		.94	.644	.619	.599

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

3. B. PTSD subtypes and Thyroid Functions:

There were no statistically significant differences between PTSD and no-PTSD group in mean levels of fT3, fT4 and TSH Table 7. PTSD subtypes: chronic, delayed onset, lifetime and those who have never had PTSD showed no statistically significant difference in mean levels of fT3, and fT4 but it was significant for TSH with higher means for life time PTSD Table 8. This is consistent with our hypothesis that thyroid functions in delayed and chronic PTSD are not different from that of participants who recovered from PTSD and participants who never had PTSD.

Tables 7. PTSD and Thyroid Functions

PTSD and No PTSD group		N	Mean	SD	Std. Error Mean
fT3 Level	NO PTSD	108	5.047	.5796	.0558
	PTSD	46	4.893	.6216	.0917
fT4 Level	NO PTSD	108	15.627	2.5191	.2424
	PTSD	46	15.524	2.8757	.4240
TSH	NO PTSD	108	1.360	1.0736	.1033
	PTSD	46	1.261	.6266	.0924

fT3: p=.861, F=.031. fT4:p=.429,F=.629. TSH: p=.367, F=.891.

Table 8. PTSD subtypes and fT3, fT4 and TSH

			Level			Total	Mean	SD
			LN	N	HN			
PTSD & fT3	Never	N(%)	0	32(36.8)	55(63.2)	87	5.01 (3.25)	.617
	Recovered	N(%)	0	8(40)	12(60)	20	4.95 (3.21)	.505
	Delayed	N(%)	1(3.3)	11(36.7)	18(60)	30	4.9 (3.18)	.692
	Chronic	N(%)	0	11(64.7)	6(35.3)	17	4.82 (3.12)	.596
Total		N(%)	1(.6)	62(40.3)	91(59.1)	154	-	-
PTSD & fT4	Never	N (%)	10(11.5)	72(82.8)	5(5.7)	87	15.51(199.67)	2.54
	Recovered	N (%)	4(20)	15(75)	1(5)	20	15.55(200.12)	2.67
	Delayed	N (%)	3(10)	26(86.7)	1(3.3)	30	15.19(195.49)	2.74
	Chronic	N (%)	5(29.4)	11(64.7)	1(5.9)	17	15.8(203.34)	2.42
Total		N (%)	22(14.3)	124(80.5)	8(5.2)	154	-	-
PTSD & TSH	Never	N(%)	20(23)	58(66.7)	9(10.3)	87	1.19	.548
	Recovered	N(%)	5(25)	12(60)	3(15)	20	1.80	1.71
	Delayed	N(%)	6(20)	22(73.3)	2(6.7)	30	1.48	.594
	Chronic	N(%)	4(23.5)	12(70.6)	1(5.9)	17	1.14	.572
Total		N(%)	35(22.7)	104(67.5)	15(10.5)	154	-	-

fT3: F=.49, p=.69. fT4: F=.169, p=.917. TSH: F=2.965, p=.035

fT3 (LN) Low Normal ≤ 3.6pmol/l (2.33 pg/ml), Normal (N) 3.61~4.89pmol/l (2.34- 3.17pg/ml), High Normal > 4.89 pmol/l (3.17pg/ml), **fT4**: Low Normal (LN) ≤13.12pmol/l (168.85ng/dl), Normal (N) 13.12~19.34pmol/l (168.85-248.9 ng/dl), High Normal (HN) >19.34pmol/l (>248.91ng/dl), **TSH**: Low Normal (LN) (≤0.74), Normal (N) (0.741~2.20), High Normal (HN) (2.201~5)

3. B. 1. Free Triiodothyroionine (fT3)

Participants with (delayed onset and chronic) PTSD showed no significant differences from those who did not have PTSD in relation to fT3 levels ($\overline{X}$ = 4.893 and $\overline{X}$ = 5.047 respectively, P=0.861 Table 7). Out of 30 participants with delayed onset PTSD, 60% had high normal levels of fT3, 36.7% were had normal fT3 levels and only 3.3% low normal levels of fT3. Of the participants with chronic PTSD, 35.3% (n = 6) had high levels of fT3, and 64.3% had normal fT3 levels. Table 8 shows that there was no statistically significant difference between different PTSD groups and level of fT3 (P 0.690). The participants with delayed onset PTSD had more high levels of fT3, while participants with chronic PTSD had more normal levels of fT3. It was observed that of the subjects who never had PTSD, had recovered from PTSD or had delayed onset PTSD 60-63% had higher levels of fT3, whereas only 35.3% of participants with chronic PTSD are having high levels of fT3. To summarize, there were an overall high levels of fT3 among the participants regardless of PTSD diagnosis, and there was no significant differences between the 3 subtypes of PTSD or between participants with and without PTSD in relation to fT3 level.

3. B. 2. Free Thyroxin (fT4) Tables

Participants with PTSD showed no significant differences compared to those who do not have PTSD in relation to levels of fT4 ($\overline{X}$ = 15.524 and $\overline{X}$ = 15.627 respectively, P = 0.429) (Table 7). There was no significant different among the four subgroups in relation to fT4 (never PTSD, $\overline{X}$ = 15.51, recovered PTSD $\overline{X}$ = 15.55, delayed PTSD $\overline{X}$ = 15.19, and chronic PTSD $\overline{X}$ = 15.8, P 0.917) Table 8.

3. B. 3. Thyroid Stimulating Hormone (TSH)

Participants with PTSD ($\overline{X}$ = 1.261) showed no significant differences with those who do not have PTSD ($\overline{X}$ = 1.36, P = 0.367) in relation to TSH levels (Table 7). Comparing different subtypes of PTSD in relation to TSH level showed a significant difference between different groups in relation to levels of TSH p=.035 Table 8.

3. C. Severity of physical injury, PTSD and thyroid function:

There was no statistically significant difference between the mean injury score for PTSD group ($\overline{X}$ = 141.24) compared to non-PTSD group mean score ($\overline{X}$ = 136.96, P=.878) Table 9. The PTSD subgroups groups, i.e., delayed, chronic, recovered, and those who never had PTSD had statistically non-significant differences in their mean score of injury score: ($\overline{X}$ = 150.28, $\overline{X}$ = 129.72, $\overline{X}$ = 108.05, and $\overline{X}$ = 150.73 respectively, P=0.573) (Table 9). Univariate analysis showed no significant difference between PTSD diagnosis, thyroid function and severity of the injury Table 10.

Table 9. Total Injury Score due to all Injuries

PTSD	Mean of total injury	N	SD	df	F	Sig.
NO PTSD	136.967	62	114.213055			
PTSD	141.240	25	124.708086	1	.024	.878
Total	138.195	87	116.603965			
Never PTSD	150.738	42	124.015550			
Recovered PTSD	108.050	20	85.980093			
Delayed PTSD	150.285	14	146.950242	3	.669	0.573
Chronic PTSD	129.727	11	94.826253			
Total	138.195	87	116.603965			

Table 10. Univariate: Total injury score, PTSD diagnosis and thyroid functions

fT3

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	1.998(a)	7	.285	.773	.612
Intercept	1698.572	1	1698.572	4600.45	.000
PTSD_No_PTSD	.003	1	.003	.008	.928
Injury Score	1.158	3	.386	1.046	.377
PTSD_No_PTSD * Injury Score	.262	3	.087	.237	.870

a R Squared = .065 (Adjusted R Squared = -.019)

fT4

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	31.205(a)	7	4.458	.664	.702
Intercept	16956.094	1	16956.094	2525.18	.000
PTSD_No_PTSD	.049	1	.049	.007	.932
Injury Score	19.749	3	6.583	.980	.406
PTSD_No_PTSD * Injury Score	6.951	3	2.317	.345	.793

a R Squared = .056 (Adjusted R Squared = -.028)

TSH

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	3.339(a)	7	.477	.419	.888
Intercept	130.192	1	130.192	114.309	.000
PTSD_No_PTSD	.027	1	.027	.023	.879
Injury Score	.282	3	.094	.083	.969
PTSD_No_PTSD * Injury Score	2.573	3	.858	.753	.524

a R Squared = .036 (Adjusted R Squared = -.050)

3. D. Severity of PTSD symptoms and thyroid functions:

Thyroid functions (fT3, fT4, and TSH) were not statistically significant in relation to severity of PTSD symptoms according to Impact of events scale (IES) and CAPS Tables 11 and 12. The fT3 levels for mild ($\overline{X}$ = 5.029), moderate ($\overline{X}$ = 5.037) and sever PTSD ($\overline{X}$ = 4.915) symptoms using IES did not show a trend of lower fT3 mean values with higher PTSD symptoms (P=.554). Free thyroxin fT4 mean levels were statistically non significant between the different levels of PTSD severity (mild, moderate, and sever) using IES $\overline{X}$ = (15.5, 15.91, and 15.35 respectively, P=0.559). There were no significant differences with the mean of TSH levels and the different levels of PTSD (mild = 1.21, moderate = 1.38, and sever = 1.44, P=0.421) symptoms severity; there was an increase in TSH mean values with increasing levels of PTSD symptoms severity. fT3/fT4 ratio were not statistically significant for different levels of PTSD symptoms severity (mild = .330, mild = .323, and severe = .328, P 0.716).

Table 11. fT3, fT4, TSH, and fT3/fT4 and severity of PTSD symptoms using Impact of Events Scale

PTSD severity IES	Thyroid	Mean	N	SD	Min	Max	df	F	Sig.
0-24: Mild	fT3	5.029	62	.6735	3.8	6.5	2	.593	.554
25-57: Moderate		5.037	51	.5517	3.5	6.0			
>58: Severe		4.915	41	.5194	3.7	6.2			
Total		5.001	154	.5946	3.5	6.5			
0-24 Mild	fT4	15.500	62	2.526	10.3	25.0	2	.584	.559
25-57 Moderate		15.910	51	2.617	9.5	22.4			
>58 Severe		15.350	41	2.790	10.2	26.0			
Total		15.596	154	2.621	9.5	26.0			
0-24 Mild	TSH	1.210	62	.6900	.0	4.1	2	.870	.421
25-57 Moderate		1.382	51	1.266	.0	8.8			
>58 Severe		1.448	41	.8734	.1	4.6			
Total		1.330	154	.9610	.0	8.8			
0-24 Mild	fT3/fT4	.33078	62	.0596	.204	.533	2	.335	.716
25-57 Moderate		.32228	51	.0493	.232	.495			
>58 Severe		.32802	41	.0558	.180	.450			
Total		.32723	154	.0551	.180	.533			

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

Table 12. Severity of PTSD using DSM-IV CAPS and thyroid function

severity of PTSD, No PTSD		f T3 Level	f T4 Level	TSH Level
Mild: PTSD Score 51-79	Mean	4.886	15.857	1.314
	N	28	28	28
	SD	.6346	2.3231	.6399
Moderate: PTSD Score: 80-108	Mean	4.830	15.700	1.120
	N	10	10	10
	SD	.6290	4.6464	.6088
No PTSD	Mean	5.044	15.524	1.352
	N	116	116	116
	SD	.5807	2.4827	1.0485

fT3: F=.169, p=.682. fT4: F=.044, p=.834. TSH F=.307, p=.581

Univariate analysis of the thyroid function in relation to the severity of PTSD symptoms and PTSD diagnosis Table 13 showed that fT3 was not statistically correlated with the severity of PTSD symptoms using CAPS, or PTSD diagnosis. No statistically significant correlations were observed between fT4, TSH, and fT3/fT4 and severity of PTSD symptoms or PTSD diagnosis.

Table 13. Univariate: Severity of PTSD symptoms, PTSD diagnosis, and thyroid function

fT3

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	1.058(a)	4	.264	.743	.564
Intercept	404.272	1	404.272	1135.64	.000
PTSD_No_PTSD	.168	1	.168	.472	.493
Severity PTSD	.122	2	.061	.171	.843
PTSD_No_PTSD * Severity PTSD	.151	1	.151	.424	.516

a R Squared = .020 (Adjusted R Squared = -.007)

fT4

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	15.111(a)	4	3.778	.543	.704
Intercept	4010.776	1	4010.776	576.631	.000
PTSD_No_PTSD	4.744	1	4.744	.682	.410
Severity PTSD	8.187	2	4.093	.589	.556
PTSD_No_PTSD * Severity PTSD	.001	1	.001	.000	.992

a R Squared = .014 (Adjusted R Squared = -.012)

TSH

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	1.529(a)	4	.382	.407	.803
Intercept	18.483	1	18.483	19.702	.000
PTSD_No_PTSD	.357	1	.357	.381	.538
SevityPTSD	.506	2	.253	.270	.764
PTSD_No_PTSD * SevityPTSD	.945	1	.945	1.007	.317

a R Squared = .011 (Adjusted R Squared = -.016)

We examined the correlations between thyroid indices and PTSD symptom severity as measured by the Impact of Event Scale IES for participants (Arousal, Avoidance, and Intrusion criteria). There were no significant differences for fT3, fT4, fT3/fT4 and TSH in relationship to total IES specific PTSD symptoms scores.

3. D. 1. Arousal symptoms

The severity of Arousal symptoms was not found to be significantly different using univariate with arousal symptoms and PTSD diagnosis Table 14.

Table 14. Univariate : Severity of Current Arousal symptoms, PTSD diagnosis, and thyroid functions

fT3

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	.563(a)	3	.188	.583	.627
Intercept	1466.826	1	1466.826	4555.91	.000
PTSD_No_PTSD	.318	1	.318	.988	.322
CurentArousal	.001	1	.001	.003	.955
PTSD_No_PTSD * CurentArousal	.205	1	.205	.637	.427

a R Squared = .015 (Adjusted R Squared = -.011)

fT4

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	6.945(a)	3	2.315	.312	.816
Intercept	14544.954	1	14544.954	1963.25	.000
PTSD_No_PTSD	.693	1	.693	.094	.760
CurentArousal	2.229	1	2.229	.301	.584
PTSD_No_PTSD * CurentArousal	.538	1	.538	.073	.788

a R Squared = .008 (Adjusted R Squared = -.018)

TSH

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	1.315(a)	3	.438	.422	.738
Intercept	112.655	1	112.655	108.393	.000
PTSD_No_PTSD	.695	1	.695	.669	.415
CurentArousal	.007	1	.007	.006	.936
PTSD_No_PTSD * CurentArousal	.492	1	.492	.474	.493

a R Squared = .011 (Adjusted R Squared = -.015)

3. D. 2. Avoidance symptoms:

There was no statistically significant difference with avoidance symptoms in relation to PTSD diagnosis and fT3, fT4, TSH and fT3/fT4 levels Table 15.

Table 15. Univariate: Severity of Current Avoidance symptoms, PTSD diagnosis, and thyroid functions

fT3

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	.431(a)	3	.144	.445	.721
Intercept	1261.627	1	1261.627	3904.40	.000
PTSD_No_PTSD	.396	1	.396	1.227	.270
Avoidance	.046	1	.046	.144	.705
PTSD_No_PTSD * Avoidance	.104	1	.104	.321	.572

a R Squared = .012 (Adjusted R Squared = -.015)

fT4

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	13.252(a)	3	4.417	.601	.616
Intercept	12450.756	1	12450.756	1693.34	.000
PTSD_No_PTSD	4.118	1	4.118	.560	.456
Avoidance	2.250	1	2.250	.306	.581
PTSD_No_PTSD * Avoidance	4.354	1	4.354	.592	.443

a R Squared = .016 (Adjusted R Squared = -.010)

TSH

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	1.318(a)	3	.439	.423	.737
Intercept	95.495	1	95.495	91.885	.000
PTSD_No_PTSD	1.040	1	1.040	1.001	.319
Avoidance	.001	1	.001	.001	.977
PTSD_No_PTSD * Avoidance	.548	1	.548	.528	.469

a R Squared = .011 (Adjusted R Squared = -.015)

3. D. 3. Intrusion symptoms:

Participants with mild intrusion symptoms compared to those with moderate and sever intrusion symptoms did not have a statistically significant difference between severity of intrusion symptoms and fT3, fT4, TSH levels and fT3/fT4 ratio. Participants with sever intrusion symptoms had higher mean values of fT3 (5.01 vs. 4.98), fT4 (16.17 vs. 15.49), TSH (1.32 vs. 1.26) Table 16. Participants with PTSD diagnosis and moderate to sever intrusion compared to non-PTSD group with mild to severe intrusion symptoms had lower $\overline{X}$ levels of: fT3 (4.92 vs. 5.44), fT4 (15.6 vs. 16.8), and TSH (1.32 vs. 1.8). All these values were in the normal range and did not show any statistical significance between the two groups Table 17. Participants in this study showed no statistically significant difference in avoidance symptoms in relation to PTSD diagnosis and fT3, fT4, TSH and fT3/fT4 levels Table 18, although the PTSD/non-PTSD difference was associated with a significant difference in fT3 levels.

Table 16. Intrusive symptoms severity (DSM-IV) and thyroid function

Current intrusion symptoms severity		fT3 Level	fT4 Level	TSH Level	FT3/FT4
mild intrusion	Mean	4.981	15.493	1.267	.326336
(n = 77)	SD	.5622	2.1118	.6171	.053103
moderate-severe	Mean	5.013	16.177	1.323	.321222
(n = 31)	SD	.6054	3.5670	.8182	.064357
df		1	1	1	1
F		.070	1.522	.147	.181
Sig.		.792	.22	.702	.671

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

Table. 17. PTSD, Intrusive Symptoms Severity, and Thyroid Function.

PTSD and intrusion symptoms severity		fT3 Level	fT4 Level	TSH Level	FT3/FT4
No PTSD mild intrusive symptoms	Mean	4.964	15.613	1.302	.3237
42	SD	.5103	2.2177	.5628	.0563
PTSD mild intrusive symptoms	Mean	4.764	15.329	1.300	.3139
14	SD	.6732	2.4241	.7596	.0400
PTSD moderate -Sever intrusive	Mean	4.927	15.609	1.327	.3220
symptoms 22	SD	.6220	2.7117	.4939	.0504
No PTSD moderate sever intrusive	Mean	5.440	16.860	1.854	.3402
symptoms 5	SD	.2702	4.1259	1.6025	.0959
df		3	3	3	3
F		1.795	.466	1.034	.29
Sig.		.155	.707	.382	.833

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

Table. 18. Univariate: Severity of Current Intrusive symptoms, PTSD diagnosis, and thyroid functions

fT3

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	2.225(a)	3	.742	2.351	.077
Intercept	1519.026	1	1519.026	4814.47	.000
PTSD_No_PTSD	2.100	1	2.100	6.657	.011
Intrusion	.958	1	.958	3.037	.084
PTSD_No_PTSD * Intrusion	1.050	1	1.050	3.329	.071

a R Squared = .064 (Adjusted R Squared = .037)

fT4

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	28.006(a)	3	9.335	1.381	.253
Intercept	15127.373	1	15127.373	2238.00	.000
PTSD_No_PTSD	17.626	1	17.626	2.608	.109
Intrusion	25.487	1	25.487	3.771	.055
PTSD_No_PTSD * Intrusion	5.414	1	5.414	.801	.373

a R Squared = .038 (Adjusted R Squared = .011)

TSH

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	.459(a)	3	.153	.327	.806
Intercept	104.896	1	104.896	224.326	.000
PTSD_No_PTSD	.335	1	.335	.717	.399
Intrusion	.316	1	.316	.675	.413
PTSD_No_PTSD * Intrusion	.252	1	.252	.539	.465

a R Squared = .009 (Adjusted R Squared = -.019)

3. E. Psychiatric Co-morbid disorders, PTSD and Thyroid functions:

3. E. 1. Generalized Anxiety Disorder (GAD) and Anxiety symptoms:

There were 5 participants with GAD diagnosis according to ICD-10 using the CIDI questionnaire. It was found that the means of fT3 ($\overline{X}$ = 5.26), fT4 ($\overline{X}$ = 17.2), TSH ($\overline{X}$ = 1.38) were higher than participants without GAD diagnosis (fT3 $\overline{X}$ = 4.99, fT4 $\overline{X}$ = 15.5842, and TSH $\overline{X}$ = 1.32). However, these findings were not statistically significant (fT3, P = .324), (fT4 P

= .165), and (TSH P = .907). fT3/fT4 ratio was not significantly correlated (P = .429 with GAD diagnosis Table 19.

Table 19. Generalized Anxiety Disorder GAD (ICD-10 CIDI) and means: fT3, fT4, TSH, and fT3/fT4

	GAD	Mean	N	SD	df	F	Sig.
ft3	No GAD	4.993	149	.5962			
	GAD	5.260	5	.5367	1	.978	.324
	Total	5.001	154	.5946			
ft4	No GAD	15.542	149	2.6235			
	GAD	17.200	5	2.2102	1	1.947	.165
	Total	15.596	154	2.6215			
TSH	No GAD	1.329	149	.9712			
	GAD	1.380	5	.6496	1	.014	.907
	Total	1.330	154	.9610			
fT3/fT4	No GAD	.32788	149	.0557248			
	GAD	.30796	5	.0311831	1	.630	.429
	Total	.32723	154	.0551520			

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

Participants with GAD and PTSD compared to those without PTSD and without GAD had higher mean values of fT3 (5.26 vs. 4.8), fT4 (17.2 vs. 15.2), and TSH (1.38 vs. 1.3) but these were not statically significant values Table 20, but this was a small group to draw a conclusion based on this small number of participants with GAD.

Table 20. PTSD with Anxiety symptoms (ICD-10: CIDI) and: fT3, fT4, TSH, and fT3/fT4

PTSD + GAD(DSM-IV: CIDI)		fT3 Level	fT4 Level	TSH Level	FT3/FT4
PTSD + GAD	Mean	5.260	17.200	1.380	.307960
5	SD	.5367	2.2102	.6496	.0311831
PTSD + no GAD	Mean	4.800	15.226	1.306	.320635
31	SD	.6372	2.5506	.6033	.0484399
No PTSD + no GAD	Mean	4.992	15.526	1.397	.328199
85	SD	.5803	2.5722	1.1102	.0577850
df		2	2	2	2
F		1.878	1.286	.095	.481
P		.157	.280	.91	.62

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

3. E. 2. Major Depressive Disorder (MDD) and Depressive symptoms:

The mean fT3 was found to be higher ($\overline{X}$ =5.2) for participants diagnosed as having MDD (according to ICD-10 using CIDI) compared to participants without MDD ($\overline{X}$ = 4.989) but this difference was not statistically significant (P = .303). fT4 mean level was found to be significantly higher ($\overline{X}$ =17.4) for participants with MDD compared to ($\overline{X}$ = 15.484, p=.033). Non-significant lower TSH level ($\overline{X}$ =0.948) was found in participants with MDD compared to participants without MDD ($\overline{X}$ =1.354). fT3/fT4 was lower ($\overline{X}$ =.3097) in participants with MDD compared to those without MDD ($\overline{X}$ =.3283) but this difference was not statistically significant (p=.330) Table 21.

Table 21. Major depressive disorder MDD (CIDI) and: fT3, fT4, TSH, and fT3/fT4

MDD		fT3 Level	fT4 Level	TSH	fT3/fT4
No MDD	Mean	4.989	15.484	1.354	.328316
	N	145	145	145	145
	SD	.5837	2.4535	.9690	.0550416
MDD	Mean	5.200	17.400	.948	.309789
	N	9	9	9	9
	SD	.7632	4.3812	.7670	.0572470
df		1	1	1	1
F		1.068	4.634	1.519	.956
Sig.		.303	.033	.220	.330

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/

Participants with (delayed onset and chronic) PTSD diagnosis and co-morbid MDD had higher means levels of fT3 ($\overline{X}$ = 5.04), fT4 (1$\overline{X}$ = 5.91), TSH ($\overline{X}$ = 1.414), fT3/fT4 ($\overline{X}$ =.3183) compared to participants with PTSD without co-morbid MDD ($\overline{X}$s = 4.82, 15.53, 1.294, and .3164 respectively) Table 22. Participants with MDD but without PTSD diagnosis (either recovered or never PTSD) had higher mean levels of fT3 and fT4 compared to participants with PTSD and MDD.

Table 22. PTSD with and without MDD ICD-10 (CIDI) and: fT3, fT4, TSH, and fT3/fT4

MDD and PTSD		fT3 Level	fT4 Level	TSH	fT3/fT4
PTSD without Depression 31	Mean	4.826	15.539	1.294	.316415
	SD	.5842	2.5985	.6055	.049095
PTSD and Depressive symptoms 7	Mean	5.043	15.914	1.414	.318386
	SD	.8404	2.6517	.6492	.030674
No PTSD and Depressive symptoms 3	Mean	5.300	20.333	.210	.279267
	SD	.6557	6.0277	.2536	.095512
No PTSD and No Depressive symptoms 113	Mean	5.039	15.466	1.365	.332022
	SD	.5776	2.4349	1.050	.056340
df		3	3	3	3
F		1.323	3.568	1.453	1.513
Sig.		.269	.016	.230	.213

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

3. E. 3. Panic attacks

In our sample we had 9 participants who, according to ICD-10 criteria using CIDI, were diagnosed as having panic attacks. There was statistical significant differences between those with and without panic attacks and the mean fT4 (P=0.002), and fT3/fT4 (=0.039) but not (fT3 p=.650), and TSH (p=.633) , we did not found this effect with PTSD diagnosis Table 23. It was observed that those with panic attacks had higher fT3 mean values (5.089 vs. 4.99), fT4 mean values (18.22 vs 15.433), and lower TSH mean values (1.18 vs. 1.34). This effect (higher means of fT3, fT4, and lower TSH) was also found in participants without PTSD with panic attacks vs. those without PTSD without panic attacks. PTSD participants with panic attacks (compared to PTSD participants without panic attacks) lower fT3 (4.8 vs. 4.87) and TSH mean (1.08 vs. 1.35), higher fT4 (17.14 vs. 15.23) Table 24.

Considering the results for fT4, the introduction of Panic Attacks as an independent variable in the analysis, led to significant effects for Panic attacks in the absence of significant differences associated with PTSD or a PTSD by Panic Attacks interaction.

Table 23. A: Panic Attacks (DSM-IV: CIDI) and thyroid function

Panic Attacks		fT3 Level	fT4 Level	TSH Level	FT3/FT4
No Panic Attacks	Mean	4.996	15.433	1.340	.329518
145	SD	.5901	2.4664	.9347	.0531232
Panic Attacks	Mean	5.089	18.222	1.181	.290411
9	SD	.6972	3.7013	1.3823	.0758673
df		1	1	1	1
F		.206	10.16	.229	4.354
P		.650	.002	.633	.039

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

Table 23. B: Univariate: Panic Attacks (DSM-IV: CIDI) and thyroid function:

fT3

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	2.161(a)	3	.720	2.080	.105
Intercept	780.235	1	780.235	2253.33	.000
PTSD_No_PTSD	2.005	1	2.005	5.790	.017
PANIC	.555	1	.555	1.603	.207
PTSD_No_PTSD * PANIC	1.192	1	1.192	3.441	.066

a R Squared = .040 (Adjusted R Squared = .021)

fT4

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	76.412(a)	3	25.471	3.918	.010
Intercept	8319.335	1	8319.335	1279.80	.000
PTSD_No_PTSD	.836	1	.836	.129	.720
PANIC	54.858	1	54.858	8.439	.004
PTSD_No_PTSD * PANIC	5.396	1	5.396	.830	.364

a R Squared = .073 (Adjusted R Squared = .054)

TSH

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	1.512(a)	3	.504	.541	.655
Intercept	52.333	1	52.333	56.152	.000
PTSD_No_PTSD	1.291	1	1.291	1.385	.241
PANIC	.002	1	.002	.003	.960
PTSD_No_PTSD * PANIC	1.069	1	1.069	1.147	.286

a R Squared = .011 (Adjusted R Squared = -.009)

Table 24. Panic Attacks, PTSD (DSM-IV: CIDI) and thyroid functions:

PTSD + Panic		fT3 Level	fT4 Level	TSH Level	FT3/FT4
PTSD + Panic Attacks	Mean	4.800	17.140	1.080	.286020
5	SD	.6964	2.1594	.3834	.0710510
PTSD + no Panic Attacks	Mean	4.874	15.235	1.355	.324174
31	SD	.6398	2.5639	.6249	.0402133
No PTSD + Panic Attacks	Mean	5.450	19.575	1.307	.295900
4	SD	.5802	5.0914	2.2047	.0924426
No PTSD + no Panic Attacks	Mean	5.029	15.487	1.335	.330972
114	SD	.5743	2.4481	1.0048	.0561871
df		3	3	3	3
F		1.52	4.153	.119	1.585
Sig.		.212	.007	.949	.195

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

3. E. 4. Alcohol Abuse:

Twenty six (16.8%) participants were using alcohol regularly in a daily basis. The levels of fT3 (4.815 vs. 5.039), fT4 (15.463 vs. 15.623), and fT3/fT4 (.3173 vs. .3292) were lower in participants using alcohol compared to participants not using alcohol but without significant difference (p=0.08, 0.779, 0.316 respectively), but there were no significant differences with PTSD diagnosis Table 25. THS levels were higher, but statistically non-significant (p=.897) in participants with regular alcohol use compared to those not using alcohol (mean 1.353 vs. 1.326). Participants with PTSD and co-morbid alcohol usage showed lower but non-significant mean levels of fT3 (4.682, vs. 4.944, P = .180) and fT3/fT4 (.3072 vs. .3233, P = .570). Alcohol as a co-morbid disorder in PTSD participants compared to PTSD participants without alcohol showed that they had higher mean levels of fT4 (15.56 vs. 15.49) and TSH (1.326 vs. 1.353) with no significant correlations P.979 and .897 respectively. Participants with co-morbid alcohol abuse with PTSD had lower mean values of fT3, but higher mean values of both fT4 and TSH. Participants without PTSD and alcohol abuse had lower mean values of all thyroid functions fT3,

fT4, and TSH Tables 26. The extent to which alcohol use in a Muslim country like Kuwait where alcohol is strictly prohibited has different implications than in secular societies where it is not.

Table 25. A: Alcohol and: fT3, fT4, TSH, and fT3/fT4

Alcohol		fT3 level	fT4 level	TSH	FT3/FT4
YES	Mean	4.815	15.463	1.353	.317312
26	SD	.3574	2.2898	.5428	.0478081
NO	Mean	5.039	15.623	1.326	.329248
128	SD	.6264	2.6913	1.0269	.0564826
df		1	1	1	1
F		3.1	.079	.017	1.012
Sig.		.08	.779	.897	.316

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

Table 25. B: Univariate: Alcohol and: fT3, fT4, TSH, and fT3/fT4

fT3

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	1.737(a)	3	.579	1.659	.178
Intercept	1981.045	1	1981.045	5675.01	.000
PTSD_No_PTSD	.643	1	.643	1.842	.177
Alcohol	.922	1	.922	2.640	.106
PTSD_No_PTSD * Alcohol	.144	1	.144	.412	.522

a R Squared = .032 (Adjusted R Squared = .013)

fT4

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	.815(a)	3	.272	.039	.990
Intercept	19810.511	1	19810.511	2828.26	.000
PTSD_No_PTSD	.065	1	.065	.009	.923
Alcohol	.377	1	.377	.054	.817
PTSD_No_PTSD * Alcohol	.045	1	.045	.006	.936

a R Squared = .001 (Adjusted R Squared = -.019)

TSH

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	2.173(a)	3	.724	.781	.506
Intercept	143.022	1	143.022	154.187	.000
PTSD_No_PTSD	.099	1	.099	.107	.744
Alcohol	.183	1	.183	.197	.658
PTSD_No_PTSD * Alcohol	1.809	1	1.809	1.951	.165

a R Squared = .015 (Adjusted R Squared = -.004)

Table 26. PTSD with Alcohol and: fT3, fT4, TSH, and fT3/fT4

PTSD and Alcohol		fT3 level	fT4 level	TSH	FT3/FT4
PTSD without Alcohol	Mean	4.944	15.493	1.244	.323362
27	SD	.6790	2.5740	.5925	.042632
PTSD and Alcohol	Mean	4.682	15.564	1.482	.307282
11	SD	.4309	2.5319	.5896	.051165
No PTSD and Alcohol	Mean	4.913	15.390	1.258	.324667
15	SD	.2669	2.1840	.5051	.045546
No PTSD and No Alcohol	Mean	5.064	15.658	1.347	.330822
101	SD	.6126	2.7332	1.1161	.059726
df		3	3	3	3
F		1.649	.063	.199	.673
Sig.		.180	.979	.897	.570

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

3. E. 5. Cigarette Smoking:

Cigarette smokers had higher levels of all thyroid functions than those who were not smokers fT3 (mean 5.117 vs. 4.891, p=.018), fT4 (mean 15.903 vs. 15.305, p=.158), TSH (mean1.36 vs. 1.302, p=.706), and fT3/fT4 (mean .3293 vs. .3252, p=.644) (Table 26). Smokers who had PTSD showed had higher level of fT3 ($\overline{X}$ = 5.015) than non-smokers with PTSD ($\overline{X}$ = 4.47, p.005). The presence of smoking was showing higher levels of thyroid hormone function: fT3, fT4, TSH, and fT3/fT4 compared to participants without PTSD and without smoking but it was statistically not significant except in the case of fT3 (p < .006, Table 27. Participants with and without PTSD with co-morbid cigarette smoking showed higher mean values of all thyroid function.

Table 27. Smoking and: fT3, fT4, TSH, and fT3/fT4

Smoking		fT3 Level	fT4 Level	TSH Level	FT3/FT4
YES	Mean	5.117	15.903	1.360	.329353
75	SD	.5672	2.7628	1.1475	.0578137
NO	Mean	4.891	15.305	1.302	.325220
79	SD	.6026	2.4622	.7488	.0527924
	df	1	1	1	1
	F	5.74	2.015	.143	.215
	Sig.	.018	.158	.706	.644

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

Table 27 A: PTSD with smoking and: fT3, fT4, TSH, and fT3/fT4

PTSD Smoking Cig.		f T3 Level	f T4 Level	TSH Level	FT3/FT4
PTSD without Smoking	Mean	4.470	14.930	1.230	.305470
10	SD	.5736	3.1059	.5229	.0374260
PTSD and Smoking	Mean	5.015	15.719	1.350	.324030
26	SD	.6044	2.3678	.6345	.0489407
No PTSD and Smoking	Mean	5.162	15.920	1.353	.333366
50	SD	.5436	2.9933	1.3386	.0622360
No PTSD and No Smoking	Mean	4.956	15.408	1.321	.327149
68	SD	.5893	2.3595	.7807	.0541175
df		3	3	3	3
F		4.511	.673	.047	.746
Sig.		.005	.570	.987	.526

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

Table 27 B: Univariate: PTSD with smoking and: fT3, fT4, TSH, and fT3/fT4

fT3

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	3.460(a)	3	1.153	3.416	.019
Intercept	2994.561	1	2994.561	8870.17	.000
PTSD_No_PTSD	1.442	1	1.442	4.270	.041
Cigarette Smoking	2.596	1	2.596	7.690	.006
PTSD_No_PTSD * Cigarette Smoking	.154	1	.154	.457	.500

a R Squared = .064 (Adjusted R Squared = .045)

fT4

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	29.283(a)	3	9.761	1.432	.236
Intercept	29230.317	1	29230.317	4289.31	.000
PTSD_No_PTSD	3.307	1	3.307	.485	.487
Cigarette Smoking	25.957	1	25.957	3.809	.053
PTSD_No_PTSD * Cigarette Smoking	13.833	1	13.833	2.030	.156

a R Squared = .028 (Adjusted R Squared = .008)

TSH

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	.878(a)	3	.293	.313	.816
Intercept	204.936	1	204.936	218.898	.000
PTSD_No_PTSD	.515	1	.515	.550	.460
Cigarette Smoking	.459	1	.459	.490	.485
PTSD_No_PTSD * Cigarette Smoking	.333	1	.333	.356	.552

a R Squared = .006 (Adjusted R Squared = -.014)

3. E. 6. Obsessive Compulsive Symptoms

In this sample 4 participants were diagnosed with OCD according to ICD-10 criteria using CIDI. These participants had statistically significant higher mean levels of fT4 compared to those without OCD (20.42 vs. 15.46, P<0.0001), but a statistically non-significant lower TSH and fT3 values Table 28.

Participants with PTSD Table 29 and co-morbid OCD showed statistically significant higher mean fT4 levels than those with PTSD and without co-morbid OCD (17.35 vs. 15.39, P<0.0001). Participants without PTSD with OCD compared to non-PTSD group without PTSD had also

higher mean values of fT4. The effect of OCD on fT4 was more pronounced in the non-PTSD group compared to PTSD group (23.5 compared to 17.35).

Table 28. OCD ICD-10: CIDI and fT3, fT4, TSH, and fT3/fT4

OCD ICD-10		fT3 Level	fT4 Level	TSH Level	FT3/FT4
No OCD	Mean	5.001	15.467	1.351	.329288
150	SD	.5917	2.4593	.9599	.0539799
OCD	Mean	5.000	20.425	.558	.250175
4	SD	.8042	4.2633	.7252	.0477492
df		1	1	1	1
F		.0001	15.231	2.685	8.405
Sig.		.996	.000	.103	.004

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

Table 29. PTSD with OCD ICD-10: CIDI and fT3, fT4, TSH, and fT3/fT4

PTSD OCD-DSM-IV CIDI		fT3 Level	fT4 Level	TSH Level	FT3/FT4
PTSD + OCD	Mean	4.650	17.350	1.050	.267150
2	SD	.7778	2.0506	.7778	.0132229
PTSD + no OCD	Mean	4.876	15.391	1.332	.321917
34	SD	.6406	2.5821	.5999	.0457707
No PTSD + OCD	Mean	5.350	23.500	.065	.233200
2	SD	.9192	3.5355	.0495	.0742462
No PTSD + no OCD	Mean	5.038	15.489	1.356	.331448
114	SD	.5743	2.4333	1.0442	.0561550
	df	3	3	3	3
	F	1.11	7.29	1.247	3.192
	Sig.	.347	.000	.295	.025

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

3. E. 7 Family History of Psychiatric Disorders, PTSD and Thyroid function:

Participants with family history of psychiatric disorders had higher mean values of fT4 (15.88 vs. 15.49) with no statistically significant difference. The mean levels of fT3 and TSH were lower in participants with family history of psychiatric disorder compared to those without family history of psychiatric disorder but it was statistically not significant Table 30. Participants with PTSD and with or without family history of psychiatric disorders had no significant differences in mean levels of fT3, fT4 and TSH levels Tables 31.

Table 30. Family history of psychiatric disorders and: fT3, fT4, TSH, and fT3/fT4

Family History of Psychiatric disorders		fT3 Level	fT4 Level	TSH Level	FT3/FT4
YES	Mean	4.958	15.883	1.116	.319535
40	SD	.6571	2.9899	.6474	.0586841
NO	Mean	5.017	15.495	1.406	.329934
114	SD	.5734	2.4861	1.0411	.0538660
	df	1	1	1	1
	F	.292	.644	2.723	1.053
	Sig.	.590	.423	.101	.306

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

Table 31. PTSD Family history of psychiatric disorders and: fT3, fT4, TSH, and fT3/fT4

PTSD and Family History of Psychiatric disorders		fT3 Level	fT4 Level	TSH Level	fT3/fT4
PTSD with no Family Psych.	Mean	4.864	15.445	1.332	.320690
History 22	SD	.5827	2.7431	.5498	.0448540
PTSD with Family Psych. History	Mean	4.838	15.592	1.323	.314531
13	SD	.7633	2.4713	.7132	.0517474
No PTSD with no Family Psych.	Mean	5.052	15.507	1.429	.332109
History 91	SD	.5712	2.4502	1.1339	.0561036
No PTSD with Family Psych.	Mean	5.021	16.004	1.012	.322425
History 28	SD	.5965	3.1856	.5909	.0614239
	df	3	3	3	3
	F	.945	.280	1.354	.637
	Sig.	.420	.839	.259	.593

fT3 pmol/l (1.54 pg/ml), fT4: pmol/l (12.87ng/dl), TSH: IU/l

4. Discussion

This study involves studying the thyroid function in 154 war injured survivors with and without PTSD. The participants were part of epidemiological sample of all war injured survivors in Kuwait after the first Gulf war in 1990-1991. We have avoided by this the possible bias (that some studies could not avoid) by recruiting control sample in a biased way. We will discuss the association between thyroid functions and PTSD according to factors studied that may play part in the activity of this hormone.

4. A. PTSD and thyroid functions:

Thyroid hormone indices were reported differently in the literature in association with PTSD i.e. different studies have found contradictory result. Our study of trauma survivors who had suffered physical trauma with consequent varying degree of physical disability showed that there was no significant difference in the total score of the injury between participants with PTSD and those without PTSD. This indicates that in our sample severity of physical trauma was not related to PTSD status. The results showed that following the cohort sample after six years (1998-2003) showed that 58 (47.2%) had no PTSD at both periods, 28 (22.8%) recovered from PTSD in 2003 they were diagnosed in 1998, 18 (14.6%) had PTSD in 2003 they were not having it in 1998, and 19 (15.4%) continued to have PTSD they were at both periods in 1998 and 2003. The cohort sample we studied from 1998 to 2003 had sustained the trauma in 1990-1991 during the Gulf war; hence all members of the sample were traumatized with varying degrees of trauma. This will make this sample unique as we saw that there were different types of PTSD (delayed, recovered, chronic) and those with no PTSD diagnosis over six years' period follow up. The results of thyroid function when interpreted should take into account this fact i.e. all were traumatized and that the psychological consequences of trauma PTSD and other co-morbid states could start at any time. Factors related to maintaining chronicity of PTSD are discussed in prevalence of PTSD section of this study.

We found that nearly 60% of the subjects had above normal mean fT3 levels. For other thyroid function variables fT4 and THS the majority of the sample was within the normal range of functioning. We found that participants with no PTSD symptoms have higher fT3, TSH, and fT3/fT4 mean levels compared to participants with PTSD symptoms. This negative correlation was also found by Haviland et al (2006) described in the introduction. Conversely participants with PTSD symptoms had higher mean levels of fT4 compared to those with no PTSD

symptoms. However, there were no statistically significant differences between PTSD and non-PTSD subjects on any of the thyroid function indices. This indicates that PTSD symptoms are not correlated significantly with thyroid function tests, although there are differences in the means for each thyroid function with PTSD symptoms. This supports our hypothesis that individuals with PTSD have different HPT axis activity throughout the course of this disorder: delayed and chronic PTSD. These results supported by the findings of Wells et al (2003) who studied thyroid function as a physiological indicator of PTSD. He found that fT3/fT4 ratio measure of thyroid function correlate poorly with self report of PTSD symptoms.

In our study we found higher mean values of fT3 for participants with delayed onset PTSD compared to those without delayed PTSD but statistically non significant. Bauer et al (1994) studying a sample of East German refugees with PTSD found a significantly higher mean fT3 levels than the control and it is in the upper middle part of the normal range and only 8% of the patients had values exceeded the upper limits. Mason et al 1996 studied the thyroid function in 11 patients with PTSD and 11 normal subjects. They found that the mean tT3 level in PTSD group was significantly elevated compared to the control group, but not fT3, tT4, fT4, TBG, TSH, T3/T4. Possible explanations for the discrepancy in the results include: degree and distress exposure, increased conversion of T4 to T3, increased thyroid hormone binding, increased peripheral catecholamine which promotes conversion of T4 to T3.The timing of thyroid sample after the trauma was variable in these studies which may had an effect on the level of thyroid hormones.

Mason et al (1994) found higher levels of this thyroid hormone among studied PTSD patients compared to controls (but still in the upper “normal range”). Higher levels of thyroid function were also been reported for fT3 by Karlovic et al (2002), Mason et al (1996), and Wang et al (1999); elevated tT4 and TBG by Mason et al (1994) and an elevated tT3/fT4 ratio by Mason et al (1994) and Wang et al (1999). These alterations in thyroid function elevations compared to non-PTSD participants were not outside of normal range. In Mason (1994) study they did not observe significant differences in tT4 level over time, but there was a persistent moderate elevation of tT4 levels. This fT4 elevation appears to be due to the greater PTSD symptom severity Mason (1994). These findings of normal thyroid functions in PTSD patients were explained by Mason as due to the “episodic fluctuations in fT4 levels on occasions”. Mason (1994) also found that the fT4/tT4 ratio is lower in the PTSD group than in the control group indicating an imbalance characterized by less fT4 more total T4 in PTSD. This could also be due

to an increase rate of conversion of fT4 to T3 as they described which supports our findings of higher fT3 than fT4 on our sample. Mason (1994) also found in the same study that the mean tT3 level is highly significant in PTSD compared to controls. In Mason's (1994) study the mean tT3 levels were in the upper part of the normal range and only 21% of the patients had values that had exceed the upper limits of normal zone. The levels of thyroid functions in our study did not exceed the upper limits of normal zone of fT3, fT4, and TSH. Mason (1994) also found that tT3 elevation in patients with PTSD is substantially greater in magnitude and frequency than the tT4 elevation which is consistent with our results that fT3 is greater than fT4. The moderately elevated tT3 levels with no elevation in fT3 levels in patients with PTSD was explained by Mason as due to an increased peripheral conversion of fT4 by deiodination to T3, or there may be an increased binding of T4 secondary to elevated TBG levels. This is supported by their observation that the PTSD groups all showed a marked and sustained elevation in levels of tT3 and fT3, as well as elevated T3/T4 ratios, supporting the increased T3 conversion hypothesis proposed.

Masson (1994) suggested that TSH levels do not differ between PTSD and control groups, and these findings are not following the neuroendocrine pathologic features of hyperthyroidism, T3 thyrotoxicosis. One explanation suggested by Mason (1994) is that the mean level for the patients with PTSD was not significantly different from that of the control group, but high levels of TBG are known to promote reverse T3 elevations. The T3 level is not low as would be expected because of the elevating effect of TBG. TSH normally contributes to 20% of the total production of T3 and it is less that likely that (normal) TSH found will explain marked T3 elevations found in PTSD. TSH does not have a prominent role in determining thyroid hormone alternations in PTSD. There is a significant negative correlation between TSH and fT4 in patients with low fT4.

Comparing PTSD and non-PTSD groups Wang et al (1999) found no elevations in tT3 and fT3 in five WWII POWs and three Korean War POWs, all with PTSD. The levels of both tT3 and fT3 levels were significantly below the control group mean. This is opposite of Mason et al (1994) findings comparing PTSD and non-PTSD groups. In our cohort sample which includes participants that all had a war related physical trauma we found what Wang et al (1999) found that fT3 was lower in PTSD. Our sample with PTSD are those with chronic and delayed onset PTSD after 13-14 years of the trauma the long period of having PTSD symptoms could explain

this. Wang et al (1999) conclude that the adaptive responses, which are partly determined by environmental constraints, may attribute to explain this discrepancy in results.

Among the three categories of PTSD (Recovered, delayed, and chronic) in our sample we found that participants with chronic PTSD had lowest mean value of fT3 with the delayed PTSD and recovered PTSD in ascending increasing order. Participants with no PTSD had the highest fT3 values. Although, there were no statistically significant differences between the four groups in this study but it was observed that the level of fT3 correlated inversely with PTSD symptoms. This is supporting our hypothesis that individuals with chronic PTSD have stable thyroid activity compared to those with acute PTSD. Bauer (1994) found low levels of thyroid function in chronic PTSD patients "other than combat related PTSD" i.e. in situations that the fight-or-flight response is not adaptive for survival e.g. in a POW situation, the Holocaust, an oppressive political situation, or some domestic abuse situations. This effect was explained by Bauer (1994) as an adaptation toward conservation/withdrawal and a resetting of the metabolic system toward conservation, anabolism, and decreased thyroid measures.

4. B. Factors affecting thyroid functions in chronic PTSD:

4. B. 1. Gender differences:

In our study we have only 2 females that had PTSD out of 5 females who participated in the study, it was difficult to do comparisons with males participated in the study because of the low number. Nevertheless compared to males in our sample had lower mean values of fT3 (4.98 vs. 5.002), TSH (1.138 vs. 1.33), and fT3/fT4 (.315 vs. .327) but with no statistical significant difference for any of these indices P.94, .619, and .599 respectively. fT4 was found to be higher in females (mean 16.08) compared to males (mean 15.57) with P.644. When comparing PTSD in males and females in our sample we found no statistically significant differences between PTSD group and non-PTSD group in relation to different thyroid indices. In spite of that females with PTSD have higher mean values of fT3 (5.048 vs. 4.853 with P.424), fT4 (15.7 vs. 15.48 with P.969), and fT3/fT4 ratio (.331 vs. .318 with P.611) and they have lower TSH mean value (1.15 vs. 1.32 with P.969). These results are consistent with the findings of Friedman et al (2005). He measured thyroid function in 63 women with PTSD due to childhood sexual abuse in comparison with a community control sample of 42 women without current PTSD. In his study women with PTSD showed significant elevations in tT3, tT3/fT4 ratio, fT3/tT3 ratio, and modest reductions

in TSH relative to control. In his study Friedman (2005) evaluated thyroid function on women and the control are also women without PTSD and childhood trauma. Our results showed that when women (the sample size is low compared to men) and men are subjected to war physical injury they have higher fT3, fT4, fT3/fT4 and lower TSH. They have the same pattern comparing women with PTSD compared to non-PTSD as was found in men. This could be explained that in our sample the mean PTSD score for women was 84.5+SD30.4, and in men the mean PTSD score was 66.97. Further more the small women sample size could be another explanation for this difference in our results. Friedman et al (2005) discussed other possible explanation for the consistent finding of elevated tT3 among women with PTSD (due to childhood sexual abuse) which could be due to excessive pituitary activity as it is marked by elevated TSH, excessive peripheral deiodination of T4 to T3 (marked by elevated tT3/fT4), or excessive production of T3 by the thyroid gland itself. But both our findings and Friedman findings on thyroid functions for PTSD women can not be generalized because of different traumatic events and sample size difference compared with males. Moreover Friedman in this study found no evidence that either previous sexual abuse without current PTSD or lifetime PTSD predicted altered thyroid activity. It is also appears that PTSD-related thyroid abnormalities are neither gender specific nor trauma specific. There was no difference in fT3 between PTSD and controls which controls TSH production.

4. B. 2. Age:

The subjects with PTSD were significantly younger than the non-PTSD group but there were no significant differences in the thyroid functions of fT3, fT4, TSH, fT3/fT4 in the groups. However, these function indices were related to age of the PTSD group. The mean fT3 and fT3/fT4 ratio levels in PTSD group were found to be significantly lower with older age. Higher but non-significant fT4 and TSH levels were observed with the older age PTSD group. These findings suggest that for the thyroid activity of PTSD patients as the age increases the activity of the pituitary increases (e.g., higher TSH with older group), increased conversion of thyroxin to triiodothyronine (low because of higher metabolism). Mason et al (1994) reported that there is elevation of tT3, fT3, tT4, (but not in elderly due to high thyroxine-binding globulin (TBG) and TBG with no elevations in fT4 and TSH in PTSD compared to control subjects. This supports our hypothesis that age has an effect on the HPT axis.

4. B. 3. Severity of the physical injury:

The levels of fT3, fT4, TSH, and fT3/fT4 were not statistically correlated with the increase in the total mean scores of injury. This supports our hypothesis that degree of disability has an impact on the HPT axis. This effect was not seen with fT4, TSH, and fT3/fT4. Mason (1996) found that T3 is not elevated (and may be decreased) in WWII and Korean War POWs with PTSD, suggesting that the elevations of T3 reported earlier in his studies may be specific to combat-related PTSD. This supports our hypothesis that the degree of disability, age, and duration of PTSD symptoms could have an effect on the HPT axis

Applying life event scale which covers life events that may be stressful during one year prior to interview to see if there is a role for recent life events stressors on thyroid function for participants with and without PTSD we found a non-statistically significant increase in the levels of thyroid hormone indices of fT3, fT4, TSH and fT3/fT4 for participants with score >300 in this scale.

4. B. 4. Severity of PTSD symptoms:

We hypothesized that individuals who recovered from PTSD have normal thyroid functions regardless of the hyperarousal, avoidance or intrusive PTSD symptoms remaining after the recovery phase. There was a non-significant but consistent trend in the relationship between thyroid function indices and the severity of PTSD symptoms. fT3 and THS were found to be higher in participants with high PTSD symptoms. Even participants without PTSD symptoms had a higher fT3 than those with mild PTSD symptoms suggesting that there could be other factors that are operating or the fT3 will not be affected unless the severity of PTSD was high enough to increase fT3. In PTSD subjects, higher fT3 levels were found with higher intensity of PTSD symptoms compared to those without PTSD diagnosis. On the other hand, fT4 showed the same non-significant but decreasing level trend with increasing severity of PTSD symptoms. Overall severity of PTSD symptoms has minimal effect on thyroid function and it is statistically non significant. Yehuda et al (1998), in their research on neuroendocrine of PTSD do not think that hypothalamic-pituitary thyroid (HPT) axis is a major stress response system in PTSD. They think that PTSD symptoms especially hyperarousal are assumed to have other neuroendocrine basis. Our findings tend to agree that thyroid function being in the normal range is not greatly affected by severity of PTSD symptoms (higher fT3, lower fT4, and lower TSH).

Our findings of a positive, but non-significant, correlation between fT3 and CAPS scores for participants with delayed PTSD vs. those non-PTSD group, and a significant trend for lifetime PTSD is consistent with Wang and Mason et al (1996) who found significant correlations between PTSD symptom severity and tT3 and fT3 among a sample of World War II male veterans with and without PTSD. Moreover we found in our study a non- statistically significant elevation of TSH in participants with lifetime PTSD and a reduction in those with delayed PTSD.

The results of the analyses for intrusion, avoidance and arousal PTSD criteria revealed that these specific symptom clusters show different trends. The pattern of thyroid functioning indices may be more related to the particular symptoms of PTSD rather than PTSD as a disorder. We found a negative but non-significant correlation between the severity of hyperarousal symptoms in PTSD and fT3, fT4, and TSH. Wang et al (1999) found a significant positive correlation between tT3, fT3, and PTSD symptoms, specifically hyperarousal. Arousal and intrusive PTSD showed opposite results i.e. higher but non-significant fT3 levels with higher intensity of the symptoms. This could be explained by the observation that arousal symptoms are not maintained totally by T3. Only intrusive symptoms showed higher mean of fT4 and TSH with higher intensity of symptoms, arousal and avoidance symptoms showed the opposite with fT4 variation with symptoms severity. None of these results showed statistical significance or were above the higher limit of the thyroid function range. In our study these figures were obtained from these participants 13 years after the trauma and the PTSD participants either having a chronic form of PTSD or a delayed form of PTSD. In the study of Wang et al (1999) it was found that PTSD victims with history of the trauma up to 50 years had thyroid function changes, and can be traced in different cultures. As in our study, Mason et al (1996) also found that thyroid elevations did not typically exceed the normal range, but there was evidence of relatively modest changes in thyroid hormone levels with a clinical significance in relation to psychiatric disorders. They also observed that thyroid alterations in PTSD may be more specifically related PTSD symptoms rather than to combat exposure alone.

The changes in thyroid functions were also noted by Karlovic et al (2002) and the results were consistent with previous reports on elevated tT3 and tT3/fT4 detected among male with combat related PTSD. In our study we found that PTSD-related thyroid abnormalities showed no consistent specificity to PTSD severity of the three clusters of symptoms. TSH was reduced in our PTSD participants but was no different from non-PTSD group since they were subjected to

the same traumatic events. This is supported by Mason et al (1999) who found no difference in fT_3 between PTSD-CSA and comparison subjects. This result is of interest but its physiological significance is unclear according to because one would expect free, not tT_3, to affect pituitary release of TSH. Published studies have had conflicting findings (Mason et al, 1999). Reist et al (1995) showed a blunted response to TRH among PTSD participants and Kosten et al (1990) found that PTSD participants resembled controls and both PTSD and control participants exhibited a greater TSH response to TRH than depressed participants.

4. C. Co-morbid Psychiatric Disorders:

In our study the effect of psychiatric co-morbid disorders in association with PTSD was tested in the same patients i.e. the presence of the two disorders and not in separate sample with isolated other psychiatric disorders.

4. C. 1. Depression

In this study presence of major depressive disorder (regardless of PTSD diagnosis) was associated with higher mean fT3 levels 5.2 pmol/l compared to those without depressive disorder mean fT3 4.989 pmol/l but without statistical significance. This is consistent with our hypothesis that co- morbid psychiatric disorders associated with PTSD had only a minor effect on HPT axis in patients with chronic PTSD. The subjects with MDD also had significantly higher fT4 levels, but lower TSH and fT3/fT4 ratio. These effects disappeared when depressive symptoms were compared using SCL-90 (i.e. participants with low vs. high depressive symptoms) this could be due to larger number of subjects diagnosed with depressive disorders using SCL-90R compared to ICD-10 criteria of CIDI. When the participants were divided into PTSD and non-PTSD group it was found that those with PTSD and MDD (CIDI) had lower fT3, TSH and statistically significant lower fT4. Our findings were consistent with Friedman et al (2004) who found that patients with PTSD and depression have no rise in tT3 than those with only PTSD, and depressive symptoms actually reduced the positive association between PTSD and elevated total T3. Friedman et al (2004) found that there is a decrease in the thyroid function for participants with depression or chronic stress syndrome; and he thinks that it is increased among both men and women with PTSD. Patients with depression or chronic stress were found by Friedman et al (2004) to have low thyroid function but the thyroid functions were among both men and women with PTSD as we found in our study for the participants with PTSD and MDD. In our sample we

did not have participants without a history of trauma hence all the participants without PTSD diagnosis at time of evaluation in our sample were liable to develop PTSD at any time in future.

Kosten et al (1990) found that PTSD patients and controls had a greater TSH response to TRH than patients with depression. They conducted a study in which TRH stimulation tests were performed on 11 patients with PTSD (6 with co-morbid major depressive disorder MDD), 18 patients with MDD, and 28 controls. Lower peak TSH response to TRH was found more in the MDD patients than in either the PTSD patients or controls, in spite of equivalent levels of depression in MDD and PTSD. Kosten et al (1990) explained this pattern of thyroid function in PTSD compared to MDD indicative of pathophysiology for TSH blunting in MDD due to altered pituitary receptor sensitivity and either hypersecretion of dopamine or hyposecretion of norepinephrine which may act through alpha-adrenergic receptors to increase TRH release leading to increased levels of TSH. This low secretion of NE in MDD patients will lead to a blunted TSH response to TRH challenge. In PTSD high adrenergic activity would stimulate TRH and subsequently TSH release. This might counterbalance any increased release of dopamine associated with the depressive symptoms in these PTSD patients. This speculation would suggest that some symptoms may have augmented rather than blunted TSH responses to TRH. This study proposed that the biology of PTSD is distinctive and in several ways opposite to that of MDD.

Goenjian et al (2003) studied 33 traumatized and 31 non-traumatized earthquake victims. They found that depressive symptoms were positively correlated with TSH, but TSH level fell within normal limits. In our study we found similar correlation with those participants with depressive symptoms according to SCL-90. The discrepancy between these result and the results of others studies was explained by Goenjian et al's (2003) that it may reflect an age-related trauma sensitive vulnerability to alteration in pituitary activity, or may be associated with co-morbid depression, as suggested by the significant positive correlation of TSH with depression, and not PTSD symptoms. In this study it was not known if TSH elevation is a primary or secondary.

4. C. 2. Generalized Anxiety Disorder:

Only 5 participants fulfilled ICD-10 criteria for GAD. These subjects with GAD showed higher means of fT3, fT4, and TSH but all within the normal limits without statistical significance. Subjects with anxiety disorders showed significant lower fT3, higher fT4, and TSH. PTSD subjects with Co-morbid anxiety disorder had non-significant but higher fT3, fT4, and TSH than those without anxiety disorder. Our results showed that the presence of co-morbid GAD will increase the thyroid gland activity in patients with PTSD but not those without PTSD diagnosis as seen from generalized anxiety symptoms alternation with thyroid function.

4. C. 3. Panic attacks

We found that mean thyroid function levels were different among participants with and without panic disorder. Significantly higher level of fT4 was found in subjects with panic disorder compared to non-panic disorder subjects. Stein et al (1988) assessed thyroid functions in 26 patients with panic disorder and 26 control subjects. They found that no significant differences in tT3, tT4, fT4, TSH, or TBG between the two groups. This study indicates that thyroid function abnormalities is not requisite biological correlate of panic disorder, normal values do not mean that patients with primary thyroid dysfunction are not predisposed to the secondary development of anxiety syndromes, and blunted TSH response to TRH is unlikely to be due to sub-clinical hyperthyroidism in panic disorder because of normal thyroid indices. In our study we had statistically significant correlations for fT4 in the PTSD group (lower mean values) and also lower fT3 and lower TSH values when PTSD and no-PTSD groups are associated with co-morbid panic attacks. This indicates that the PTSD operates to mediate these symptoms.

4. C. 4. OCD

The small group of OCD diagnosed cases had higher fT4 (statistically significant) and lower TSH levels compared non-OCD subjects. There were no differences between these groups for fT3 function. McCracken et al (2005) examined sixteen OCD children and adolescents with 13 control children and adolescents without psychiatric illness on basal measures of thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4). They found that OCD subjects demonstrated subtle but significant elevations of TSH, T3, and T4 and they conclude that elevated thyroid function may reflect aspects of the underlying pathophysiology of OCD.

Hantouche et al (1991) found evaluated thyroid function (T3, T4, TSH) and TRH test in 17 patients with obsessive-compulsive disorder not associated to major depression. Aizenberg et al (1991) stimulated serum thyroid stimulating hormone (TSH) with 200 micrograms of thyrotropin releasing hormone (TRH) in 10 patients with OCD and in 10 control subjects. They found significantly more blunted TSH responses among OCD patients than control subjects. They conclude that there may be a dysregulation of the hypothalamic-pituitary-thyroid axis in OCD. We found that the elevated fT4 in our sample is consistent with previous studies. fT3 was not elevated in our sample which could be explained by the multiple psychiatric co-morbidity in our sample. When combined with PTSD participants with OCD and co-morbid PTSD showed the same results i.e. still having statistically significant higher fT4, lower TSH, and lower ratio of fT3/fT4.

4. C. 5. Alcohol Use

In our sample 26 subjects were using alcohol and they had statistically significant lower fT3, non-significant lower fT4, and a non-significant higher TSH. However, for subjects with PTSD with co-morbid alcohol use the thyroid function indices did not show any statistical significance for those with and without alcohol use both groups were having constantly lower fT3 in both groups (PTSD and non-PTSD), still higher fT4 in the PTSD group but it lost this effect in the non-PTSD group, and still higher TSH levels in the PTSD group. Karlovic (2004) did not find any significance for the presence of alcohol co-morbidity that may affects thyroid function. He studied the possible effect of alcohol on thyroid function in 41 chronic PTSD with co-morbid alcohol dependence and 59 healthy controls in Croatian soldiers. He found that participants with chronic PTSD with or without co-morbid alcohol addiction had significantly higher values of tT3 than the control group and there was a significant correlation between tT3 levels and number of traumatic events in both the PTSD group and those with PTSD co-morbid with alcohol dependence. He also found a significant correlation between tT3 levels and symptoms of increased arousal in both PTSD and PTSD co-morbid with alcohol dependence.

4. C. 6. Tobacco Smoking:

Schlienger et al (2003) investigated the effects of smoking on the thyroid gland and concluded that the consequences of smoking on thyroid function and its size are controversial. They reported that (1) the increase in serum thyiocyanate (a potent inhibitor of iodine transport) may

contribute to the development of thyroid dysfunction, (2) smoking is associated with normal thyroid hormone levels, with a tendency to lower TSH levels and enlargement of thyroid size, (3) there is an increased risk of developing overt thyroid disease, (4) smoking decrease both thyroid secretion and thyroid hormone action, but hypothyroidism does not appear to be more frequent, (5) smoking increases the metabolic effects of hypothyroidism. We found that smokers diagnosed with PTSD compared to smokers without PTSD had significantly higher levels of fT3, and higher mean levels of fT4, and TSH. The same differences were observed in non-PTSD group smoker compared to non-smokers. In our sample the higher activity of thyroid gland observed in smokers could be attributed to other factors than stated in Schlienger study in trauma survivors. This could be due to the sustained effect of the trauma on the HPT axis which makes the thyroid gland sensitive to the effect of smoking in the presence of other physical and psychological disturbances associated with PTSD.

4. D. Summary of the results:

Table 32. Summary of the findings: PTSD and no-PTSD groups and different variables
* p<.05 **p<.001

Comparison Groups	Mean Thyroid Hormones Levels						PTSD			No-PTSD		
	fT3	fT4	TSH	fT3	fT4	TSH	fT3	fT4	TSH	fT3	fT4	TSH
1. PTSD 2. No-PTSD	4.89	15.52	1.26	5.04	15.62	1.36	-	-	-	-	-	-
1.Delayed and 2.Chronic PTSD *	4.9	15.19	1.48	4.82	15.8	1.14	-	-	-	-	-	-
1. Injury score ≤43 and 2. Injury score 106-230*	4.97	15.74	1.30	5.02	15.12	1.27	5.08	15.33	1.25	4.92	15.9	1.32
1.Mild PTSD CAPS 51-79 2.Moderate PTSD CAPS 80-108	4.88	15.85	1.31	4.83	15.7	1.12	--	-	-	-	-	-
Severe Avoidance CAPS >12.5	4.94	15.13	1.25	4.96	15.84	1.37	4.89	14.88	1.04	5.12	16.5	1.9

Table. 33. Summary of the findings: PTSD subtypes and different variables

	Variable						PTSD			No-PTSD		
	1 Yes			2 No								
	fT3	fT4	TSH	fT3	fT4	TSH	fT3	fT4	TSH	fT3	fT4	TSH
Severe Arousal CAPS >12.7	4.88	15.33	1.24	4.98	15.85	1.39	4.84	15.3	1.12	4.92	15.6	1.62
Severe Intrusion CAPS >8.4	5.01	16.17	1.32	4.98	15.49	1.26	4.92	15.6	1.32	5.44	16.8	1.85
Severe ADLs impairment	4.83	15.51	1.22	5.07	15.52	1.21	4.67	15.75	1.00	4.99	15.2	1.44
Severe physical symptoms	5.01	15.41	1.42	4.95	15.77	1.26	4.95	15.91	1.25	4.94	15.6	1.27
Moderate psychoticism (EPQ)	4.81	15.42	1.79	5.00	15.6	1.3	4.92	15.57	1.25	4.6	15.1	2.8
Severe Neuroticism* (EPQ)	4.98	15.98	1.48	5.03	15.61	1.26	4.86	15.64	1.3	5.03	15.7	1.98
Severe Extraversion (EPQ)	5.01	16.04	1.25	5.14	16.37	1.55	5.02	16.97	1.57	5.00	15.4	1.23
High Pulse rate	5.07	16.04	1.2	4.96	15.36	1.39	4.93	15.92	1.13	5.09	16.1	1.24
Systolic BP	5.01	15.57	1.41	5.06	15.94	1.29	4.71	15.27	1.24	5.06	15.5	1.76
High BMI O-III *	4.83	14.83	1.19	5.06	16.86	1.29	4.76	14.85	1.4	4.99	15.1	1.34
High WHR *	5.01	15.49	1.35	4.93	16.04	1.2	4.84	15.45	1.41	5.00	15.5	1.34
LES score >300	5.05	15.8	1.41	4.97	15.47	1.28	4.97	15.33	1.38	5.09	15.9	1.56
GAD- ICD-10	5.26	17.2	1.38	4.99	15.54	1.32	5.26	17.2	1.38	-	-	-
Anxiety- SCL-90*	4.94	15.98	1.65	5.01	15.49	1.24	4.68	15.54	1.34	5.1	16.3	1.92
Depression – SCL-90R	4.9	15.99	1.41	5.04	15.44	1.29	4.76	15.35	1.33	5.03	16.6	1.5
MDD – ICD-10 *	5.2	17.4	0.94	4.98	15.48	1.35	4.82	15.53	1.29	5.3	20.3	0.21
Panic attacks **	5.08	18.22	1.18	4.99	15.43	1.34	4.8	17.1	1.08	5.4	19.5	1.3
Alcoholism*	4.81	15.46	1.35	5.03	15.62	1.32	4.68	15.56	1.48	4.91	15.3	1.25
Cigarette **	5.11	15.9	1.36	4.89	15.3	1.3	5.01	15.71	1.35	5.16	15.2	1.35
Psychoticism**	4.94	15.62	1.91	5.01	15.59	1.23	4.84	15.38	1.54	5.01	15.7	2.16
Somatization	4.99	15.93	1.25	5.00	15.55	1.33	4.84	16.0	1.31	5.32	15.6	1.10
OCD- ICD-10**	5.00	20.42	0.55	5.00	15.46	1.35	4.65	17.35	1.05	5.35	23.5	.065
OCD-SCL-90*	4.94	16.82	1.42	5.0	15.45	1.31	4.86	15.75	0.49	4.9	17.0	1.47
Hostility *	5.08	16.09	1.83	5.0	15.55	128	4.93	15.5	1.58	5.12	17.0	2.22
Family Psychiatric History	4.95	15.88	1.11	5.01	15.49	1.40	4.83	15.59	1.32	5.02	16.0	1.01

* $p<.05$, ** $p<.001$

Boneferonni coefficient the used for the above 25 variables, so the corrected p value is .00205. Any test with a p value less than .02 is significant at the 5% level.

Summary

1. The thyroid function changes in association with PTSD in this study did not reach the hyper or hypothyroid states that necessitate pharmacological intervention. All the changes are within the "normal range".

2. The minor thyroid function alternations in chronic war related PTSD appear to be chronic, and could be detectable years after the war as this disorder changes with life-time of the survivor and the chronic nature of this disorder. Because of the sensitive nature of the thyroid gland (the hormones released), the complex factors related to PTSD symptomatology and that many factors could affect thyroid function the levels of these hormones vary from one PTSD participant to another depending on how many factor he /she has that could affect the function of this gland including factors that previously not considered like cigarette smoking and personality traits and co-morbid disorders.

3. In general the trend of thyroid function in association with PTSD (delayed and chronic) compared to no PTSD status is lower fT3, and TSH and higher fT4 levels. It was observed that fT3 was higher in participants with delayed onset PTSD compared to participants chronic PTSD.

4. Females with PTSD (compared to males with PTSD) had higher mean score values of PTSD symptoms severity which is not related to severity of total scores of trauma. Females with PTSD have higher fT3, fT4, fT3/fT4 ratio and lower TSD compared to males with PTSD, but it is statistically non significant.

5. fT3 was found in higher level (as the normal range of this hormone) in the studied sample which represents trauma survivors as 60% of the sample were in the high normal range. This was not observed for fT4 and TSH as the majority of the studied samples were having normal values of these hormones.

6. The only significant difference comparing thyroid function PTSD and severity of trauma score, it was fT3 (the higher severity of trauma score with PTSD the higher fT3 mean values).

7. Overall with increased severity of PTSD “symptoms” for the sample (without dividing PTSD and non-PTSD) it was found TSH was showing higher values, fT4 and fT3 was increasing to a higher reached level. With PTSD diagnosis the more sever PTSD symptoms caused higher fT3, lower fT4 and TSH.

8. With higher arousal symptoms there were lower rates of mean values of thyroid hormones fT3, fT4, and TSH. Among PTSD participants with higher arousal symptoms compared to lower arousal symptoms they have higher fT3, and lower fT4 and TSH.

9. The overall severity of avoidance symptoms had higher fT3, lower fT4 and TSH. With PTSD diagnosis the more sever the voidance symptoms the higher mean fT3, lower TSH and no change in fT4.

10. The higher the intrusive symptoms the higher rate of all thyroid hormones tested fT3, fT4 and TSH, which are also consistent with PTSD diagnosis.

11. The presence of general health problems that is affecting work and daily activities had lower the mean values of fT3, fT4, and TSH in participants with PTSD compared to those without PTSD diagnosis.

12. Participants with personality traits: Psychoticism (higher fT3and fT4, lower TSH), Neuroticism (only higher fT4 levels) and Extroversion / introversion (higher mean rates of all thyroid functions: fT3, fT4, and TSH)

13. PTSD participants with higher pulse rates they were having higher mean rates of fT3 and fT4 and lower TSH. The higher the blood pressure values in PTSD the mean values of all thyroid functions of fT3, fT4, and TSH. The higher BMI values with PTSD diagnosis the lower fT3, and fT4 and the higher TSH mean values. The same effect was found in relation to waist-hip ratio WHR

14. Participants with higher scores (>300) of life events in association with PTSD they have higher mean rates of fT3 and TSH and lower fT4.

15. Generalized anxiety disorder GAD in participants with PTSD caused higher mean values of fT3, fT4, and TSH.

16. Major depressive disorder MDD with PTSD diagnosis has caused higher mean values of fT3, fT4 and TSH.

17. Panic attacks with PTSD had increased mean levels of fT4 and lower TSH , but they have the same levels of fT3 (for participants with PTSD without panic attacks).

18. Alcoholism in association with PTSD had lower fT3, higher values of fT4 and TSH. Cigarette smoking with PTSD diagnosis had higher fT3 and TSH and lower fT4 levels.

19. Obsessive compulsive disorder OCD in association with PTSD had lower fT3 and TSH and higher fT4 mean values.

20. Family history of psychiatric disorders has no effect on thyroid functions in PTSD participants.

VII. Limitations and Strengths of the Study

The strengths and limitations of this study should be considered to determine the extent that the findings can be generalized and how they can inform the literature generally.

1. Limitations of this study:

One issue which limits the interpretation of the findings of this study is the lack of a comparison control group who were not traumatized. The importance of such control group that it would clarify the role of physical injury in the neurobiology of PTSD. This limitation was also observed in many studies in the literature which had focused on the trauma survivors without having a control sample of non-trauma participants, Yehuda R et al (2007-a), Roth G et al (2006) and Otte C (2005). Wherever possible normative data from the Kuwaiti population was used to provide contrast information, but this is not a complete substitute for a concurrently assessed contrast group.

The fact that they were all injured is a limitation as there was no comparison with combat non – injured as with other studies evaluating PTSD in combat related veterans.

Kuwait is a relatively a small country with total population size of 0.75 million at time of war: of these >20,000 were POWs, >1,200 were executed, and half of the population were deported from Kuwait during the occupation period, Al-Hammadi et al 1994. The population norms for Kuwait have been skewed by the fact there was a high level of trauma exposure of most of the population as a response of the war. These large numbers may have led to society wide issues that affected the outcome for those at risk for PTSD.

This study shares concerns what has been discussed in the literature surrounding ‘delayed onset PTSD’. These concerns are minimal in this study for the following reasons. All the participants in this study have serious physical injury resulted in a physical disability. In addition the symptoms were related to the physical injury during the assessment which was face to face interview. Furthermore more than one assessment was done with different methods: clinical and using scales and questionnaires.

PTSD develops as a consequence to exposure to a traumatic event with actual threatening or serious injury or threatening to the physical integrity of self or others that is associated with intense fear helplessness or horror, DSM-IV-TR APA (2000). Based on this definition war trauma is one of the wide ranges of other traumas that can predispose to PTSD. War trauma that includes physical disability (that works as persistent continuous reminder of war) and torture (works as continuos cognitive reminder of imprisonment) both of which may contribute to the chronicity of post-war PTSD symptomatology. In our study the sample was from the war trauma category. This could be another limitation as that the sample is not representative for PTSD in general, since it included only PTSD as a consequence of war (due to physically injury among veterans). Although the study is a prospective study design for the course of PTSD a homogenous samples in terms of trauma: i.e. war combat injuries and disability related to that history, this may limit generalizability of results to other, more heterogeneous trauma populations in general. The females who participated in the study were very few; this is due to the low number of females who participated in combat in the Kuwait army. This makes it difficult to generalize the results of this study on females with PTSD due to combat.

The sample was not randomly selected, but it involves all officially registered war injures survivors after the first Gulf war 1990-1991. Since the subjects represent 100% of a clearly defined population, the question of sampling is moot. This is essentially the entire sample of those who were injured. This completeness is very unusual as such groups would usually simply be recruited from a clinical service where it is very difficult to know who they represent unless they are recruited at the time of injury which is the case with many of the larger prospective studies of motor vehicle victims.

The blood samples drawn in this study was done 12-13 years after the original (war) trauma, hence only subtypes of chronic PTSD were studied in relation to thyroid functions alternations: recurrent chronic, delayed, and recovered type of PTSD. This study is different from other studies done e.g. in the first year after the traumatic exposure. The dysregulation in the neuroendocrine pathway would be more apparent after the initial trajectory for the onset of PTSD. The cortisol level taken in this study is a single am assessment (only one measure of morning cortisol was obtained) this could miss other periods of the day that involves variation in the circadian rhythm which involves variable levels in which other studies found differences and the equalize (PTSD and no PTSD trauma survivors, de Kloet CS, 2007.

The subjects in this study may be considered to have reached a state of allostasis. Allostasis is the process of achieving stability, through physiological or behavioral change which can be carried out by means of alteration in HPA axis hormones, the autonomic nervous system, cytokines, or a number of other systems, (that works as in a nonlinear network and reciprocally regulate each other) and is generally adaptive in the short term, McEwen at al (2003). Furthermore McEwen (2003) stated that it is the duration of the illness and not the age of the subjects that predicts a progressive reduction in volume of the hippocampus, determined by structural magnetic resonance imaging. Moreover the maintenance of homeostasis is an active process that requires the output of mediators such as those of the autonomic nervous system, and the neuroendocrine and immune systems, this is process is "maintaining homeostasis through change McEwen at al (2006). The permanent changes seen in brain specifically amygdala and hippocampus as a consequence of this process leads, over time, to wear and tear on the body ("allostatic load"). This concept could be important for physically injured war survivors with permanent physical disability with subsequent chronic PTSD. These participants with chronic PTSD had adapted to these changes and reached to this stage of homeostasis as indicated by the low cortisol level after more than 10 years of the traumatic experience and maintaining the same level of PTSD symptomatology as tested 5 years interval between the first and the second assessment.

The absence of difference between the injured individuals with and without PTSD subjects represents an interesting difference from other findings. Given that these people sustained what were generally substantial injuries, it raises the question as to whether some of the differences that have been previously ascertained in the inter-current function in PTSD may be in fact be accounted for by the variability in concomitant physical injuries. Hence the deficiency of this study was the lack of having an uninjured comparison group with equal combat exposure.

Many of the analyses used are categorized rather than continuous statistical methods. As a consequence some important relationships may have been missed. The use of predominantly Chi-Square rather than odds ratios may contribute to this. Multiple correlations were corrected statistically may be another contributory factor. The use of Chi-Square also limited the ability to convey for a number of the interactions. While these have been modeled in these categorical comparisons, this could be a limitation as it is not being consistent with current statistical practice. For publication further analyses will be used to examine for interactions which were not investigated as part of the current thesis.

In our study we faced the problem of multiple comparisons (also known as multiple testing problems). This has occurred because we have subjected a number of independent variables to the same criterion that would be used for a single variable. As the number of independent variables of the acceptance criterion begins to outweigh the high unlikelihood associated with each individual test, it becomes increasingly likely that one will observe data that satisfies the acceptance criterion by chance alone (even if the default assumption is true in all cases), Abdi et al (2007). He described that these errors could be considered false positives because they positively identify a set of observations as satisfying the acceptance criterion while that data in fact represents the null hypothesis. It represents as the potential increase in Type I error that occurs when statistical tests are used repeatedly: If *n* independent comparisons are performed, the experiment-wide significance level α (alpha) is given by

$$\alpha = 1 - (1 - \alpha_{\text{per comparison}})^{number of comparisons}$$

and it increases as the number of comparisons increases. If we do not assume that the comparisons are independent, then we can still say:

$$\alpha \leq \alpha_{\text{per comparison}} \times number of comparisons$$

There are many mathematical techniques have been developed to counter the false positive error rate associated with making multiple statistical comparisons. In our study we have used Benferroni correction.

Although the history of use of psychotropic medications were taken, the impact of this was not looked for due to the fact that the history was not complete as many of the participants did not know the type, no medical records were available and some chose not to declare their use.

The other limitation is that a dexamethasone suppression test was not done and hence the reactivity of the HPA axis has not been explored.

2. Strengths of the study:

One strength of the study is the fact that the sample represents all the registered injured survivors i.e. representing the population of physically injured in Kuwait after the First Gulf War.

This sample is an epidemiological sample covering injured survivors of Gulf War. The most important strength of the study is that this study is a cohort study following war injured victims for a 5 year period for PTSD symptoms and biological assessment in the second assessment. The effects of the long duration of PTSD symptoms made this sample unique regarding the impact of chronicity of PTSD symptoms on the biological parameters in PTSD war survivors. Another factor which gives strength to the study is that there was no financial or compensation benefits for any of the subjects that may contaminate the sample. Furthermore the social stressor was removed after the war e.g. issues related to work and social support after the war.

The sample in this study is a complete sample of more severely injured people and not just a treatment seeking population which is much of the neurobiological reported research of PTSD. The time between trauma and assessment was 12-13 years which was relatively a long period of time to study hormonal changes in chronic PTSD.

This study explored the changes associated with PTSD in culturally homogeneous sample - no immigrants were involved. In this study the sample shows the effect of the ongoing effect of the hostility in the region and its effect in the PTSD.

The inter-rater reliability for diagnosis of PTSD in Kuwait population was tested in other studies. In these studies that involved: an epidemiological study for the population, study on the martyrs families and a study on the firefighters the inter-reliability in PTSD diagnosis was tested using the measures and face to face clinician interview. These issues were discussed and monitored by the supervisors of this study.

This study done in a 3rd World-Arabic culture, the individuals demonstrated substantial rates of PTSD independent of the factors that are often are viewed to be pertinent determinant of emergence of symptoms, namely issues related to compensation. This is significant in this sample to detect PTSD. This study also demonstrated the validity of the construct of PTSD in a Muslim-Arabic culture. After the formal recognition of PTSD in 1980 its international

acceptance was not rapid or without controversy. Jones et al (2007). Rosen et al (2007) raises an important issue in regarding the validity of the basic assumptions in PTSD. He discussed the comments in the media on how debate surrounding PTSD has become heavily political in nature. The following issues were summarized by Rosen et al 2007 from the literature that challenges PTSD construct:

-PTSD represents a paradigm shift that has altered our cultural narratives for explaining human responses to adversity
-The core assumptions and hypothesized mechanisms underlying the diagnostic construct of PTSD have not been supported; research and clinical issues have impacted the PTSD database; and serious concerns continue with regard to the construct's basic validity and clinical utility
-The concerns with regard of social and political origins of the diagnosis
-After nearly 25 years of research and clinical experience, there is little about the diagnosis that has gone unchallenged."
-It is premature on scientific grounds and actively harmful on ethical grounds to disregard the diagnosis of PTSD
-Victims of trauma want professionals to advance their knowledge so that accurate information, sound advice, and non-harmful interventions develop over time.

The results of this study of the rate of PTSD suggest that PTSD is a universal disorder and is relatively independent of the individual's culture or spiritual belief. These will provide important insight into the biological underpinning of this condition. This study demonstrated the ongoing suffering and morbidity of these individuals despite the lapse of time since the end of the conflict.

The issue of the restriction of alcohol in Kuwait and the low prevalence of the usage compared to other populations makes this sample unique. Furthermore although consumption of alcohol is legally restricted, 16% of the sample was drinking alcohol indicating the extreme end of severity they have reached as alcohol is very difficult to obtain locally.

3. Future research:

There are still many questions not answered in PTSD. In reviewing the literature in this study it was obvious that we need to increase our knowledge in the uncertainties aspects of PTSD. Future research should look for the following aspects of neurobiology of PTSD to explain the current literature findings:

In this study although we found that most of the sample had low levels of cortisol, the participants with delayed onset PTSD had significantly lower cortisol level, and we observe it in participants who did not develop PTSD. The question for future research is why this difference exists? This was also raised by Delahantya et al (2006) regarding why neurobiological changes observed not in all persons who develop PTSD and others who do not develop PTSD (all were subjected to the same traumatic events).

Our sample concentrated on war injury, and involved few female participants. For future research in this field choosing participants with disability due to civilian accidents and those with disability to disease e.g. amputations due to medical causes may further clarify the role of trauma. In this study we were not able to have access to the predeployment information for the veterans who participated in the study. The type, level and duration of military training history were not obtained. We did not include veterans that were not injured which could be also incorporated in future studies. The importance of this issue was also highlighted by Ikin et al (2005).

The environmental factors after the 1st Gulf war could have affected other systems beside the endocrine system. The fumes of burning oil wells, the effects of war operations on the population of the Gulf has been not yet investigated. Future studies that are designed to investigate e.g. the immune system could contribute to the knowledge of the chronicity pattern seen in PTSD. This was also suggested by de Kloet et al (2007).

PTSD has high comorbidity with other psychiatric disorders; major depression is one of these disorders which we found in our study of high comorbidity. Studies suggest that patients suffering from comorbid PTSD and depression differ clinically and biologically from individuals with PTSD alone or depression alone Sher et al (2005). Future studies designed to categorize the chronological development of these comorbid disorders with PTSD with neurobiology of these disorders alone or with association with PTSD. This will clarify this association and the role of

environmental and genetic factors in the etiology and pathogenesis of stress-related disorders, but also be useful in refining conceptions of stress-related disorders themselves and possible approaches to the treatment of these conditions.

4. General challenges in doing neurobiology research in PTSD:

There are multiple challenges facing neuroendocrine studies in PTSD. Methodological considerations and study design could be the most important. Separating demographic, genetic, physical, social, and psychological factors that may contribute independently is a challenge that faces future studies, and/or in identifiable, patterns toward various clinical outcomes in PTSD including the neuroendocrine effects.

The present Diagnostic and Statistical Manual of Mental Disorders, (DSM IV-TR) does not include PTSD subcategories: mild, moderate, or severe and trauma survivors that do not meet full criteria (Subsyndromal). This re-evaluation is important based on current available clinical understanding of the effect of stress and its consequences.

Sautter et al (2003) proposed the following needs for assessments of PTSD:
(1) Comorbidities of Axis-I, II and III disorders in the subjects:

The results of neurobiology studies on PTSD e.g. could be affected by the impact of depression on CRF, because patients with major depression show higher levels of CRF than control subjects.

(2) The number and quality of prior traumatic exposures, since the experience of one exposure may modify the quality of response to the next.
(3) The family's coping styles for dealing with trauma.

One of the challenges on current neurobiology study of PTSD is the sample sizes. Relatively small sample sizes limit the power to detect group differences and also limit the generalizability of the findings, Sautter et al (2003).

This may be even more difficult if the participants in the study had received secondary gain for the participation in the study or they are anticipating a secondary gain or compensation such as in the military and combat related trauma. One important issue in challenging research among veterans with PTSD is the possible influence of compensation-seeking participants on the assessment and severity of reporting PTSD symptoms, Fontana et al (1998) reported mixed results in this issue.

PTSD is associated with sleep disturbances Harvey et al (2003), and substance abuse Southwick et al (2001) including alcohol abuse. This may constitute a challenge for neuroendocrine studies design.

Another challenge is the type of study design Vogt et al (2007):
- Most of the study designs are cross-sectional and dependent on retrospective self-reports. An excellent next step would be to combine the strength of SEM (structural equation modeling procedures to examine the complex interplay among predeployment, war-zone, and postdeployment factors) with a longitudinal design that allows for greater certainty regarding the directionality of relationships among key variables: earlier life events.
- Reliance on self-reports may also be problematic for reasons of method covariance (i.e., effects may be overestimated) and response bias (e.g., malingering).

Golier et al (2006) suggested that one of the problems faced in doing research in this field is the presence of an unmeasured factor (e.g. caffeine intake, alcohol intake) which may contribute to the neuroendocrine differences.

de Kloet et al (2007) had identified two challenges in conducting neurobiological studies in patients with PTSD. These include:
- Compliance of the subjects with the tests is a problems facing research in this field.
- Major depressive disorder (MDD) which is prevalent in a high number of patients with severe PTSD, exclusion of patients with a comorbid MDD would imply that only patients with mild PTSD will be included.

- Early life trauma has been shown to affect HPA axis functioning significantly. This was also suggested by Yehuda et al (2004) about the role of prior trauma on HPA axis functioning and indicates that neurobiologic sensitization of the HPA axis in response to trauma may be a prominent neuroendocrine response in major depression even in the absence, but certainly in the presence, of PTSD.
- The inclusion of a non-military healthy control group makes it impossible to differentiate between the relative contributions of trauma exposure versus other military related factors e.g. military training and deployment military personnel are frequently exposed to psychological and physical stress and are trained to sustain high levels of alertness. This might imply that enhanced suppression of cortisol in veterans may also be related to military training.

Fiedler et al (2006) stated the following challenges must be faced research in PTSD:
- That when the overall response rate of the target population is suboptimal to participate in the study, this may attenuate the generalisability of the study
- The psychiatric diagnoses remain provisional using rating scales, if the interviews were conducted by lay interviewers rather than trained clinicians, this will minimize reliance on clinical judgment.

Zahava et al (2007) discussed one diagnostic challenge in PTSD which is the definition of dysfunction and distress. This may influence inclusion criteria according to the DSM criteria.

There are differences in cortisol levels between trauma exposed with and without PTSD and also with non-traumatized controls, this is a challenge for future research in determining the appropriate comparison subjects for studies of the neuroendocrine correlates of psychiatric disorders Yehuda et al (2004). Furthermore Yehuda et al (2004) set this as a fundamental issue in interpreting the results to the extent that shifts in the type of comparison subjects can alter the nature of the findings with respect to group differences, dissimilar conclusions may emerge. The challenge is the comparison group as possibly contributing to variance within trauma survivors.

Yehuda et al (2004) considered the type of statistical approaches used and dependent variables chosen to express biologic change may also impact substantially on how conclusions with respect to group differences are made.

Yehuda et al (2007-b) presented other challenges for research in this field:

- The hippocampal volumes (constitutional risk factors) are associated with risk and/or resilience factors in PTSD, and are associated with accelerated age-related decline in PTSD. PTSD may reflect an interaction between biologic correlates associated with both constitutional and environmental risk factors. These may be influenced by the developmental stage at which trauma occurs, and/or the age or life stage of the individual. These are important factors in designing future studies.

Studies done years after the trauma may have different risk factors form the initial posttrauma period as suggested by Schnurr et al 2004, Koenen et al (2003). This may affect the neurobiology of PTSD and is a challenge for future studies.

Golier et al (2006) indicated in his study on Gulf war veterans that further work is needed to distinguish among the possible mechanisms of enhanced cortisol suppression in Gulf War veterans and to determine the extent to which dysregulation of the HPA axis is associated with deployment exposures and poor health outcomes in these veterans.

5. Significance and implications:

PTSD following the first gulf war was studied in the troops that came and participated in that war. Few studies performed among soldiers from the gulf countries who participated in this combat:

A. Kuwaiti veterans were subjected to an enormous trauma due to combat and torture as POWs.
B. This was further magnified by the trauma to other members of the family and or relatives and friends including execution.
C. The experience in this sample is unique as
1. Multiplicity of the trauma including physical injury
2. Voluntary participation, without compensation
3. Cohort sample
D. The sample was subjected to the fumes of burned oil for the 10 months period of the burn Feb-Nov 1991.

In Kuwait as in many other 3rd world countries the research in this field (PTSD) is so sparse inspite of being in the middle of the most dangerous spots in the world at this time. One factor that contributes to this is funding. Another is the acceptance by the health authority as a priority and by the legal authority (in case of veterans) as a possibility to do it (confidentiality of the information).

This study showed that PTSD is still prevalent in Kuwait population after 13 years of the end of 1st Gulf war, inspite of the great efforts of the Kuwait government after the war to support the population financially and the psychiatric facilities to deal with PTSD after the war. At this level of PTSD in the veteran population the veteran's health services should be aware of the consequences of PTSD among veterans. The high comorbidity of PTSD both psychiatric disorders and physical disorders should alert the family practise to this disorder in a country that was totally invaded and occupied for seven months.

Engel et al (2000) raised one important issue that is being observed in PTSD veterans of the 1st Gulf War. He stated that "although a great deal of empirical research consistently implicates PTSD as an important cause of physical symptoms, it seems clear that there are other important and potentially Gulf War–related causes of physical symptoms among ill Gulf War veterans" whether psychological causes or environmental exposures experienced during and possibly immediately after the Gulf War. In Kuwait so far there is no, published study about the chemical involvement in Kuwait veterans. In this study we cannot ignore the fact that the participants in this sample were exposed to oil fire fumes which was exposed by the 0.75 million of Kuwaiti population yet the rate of PTSD in the population is not greater than that found in this sample. From the study on this sample the physical and the psychological factors are the main factors that contribute to PTSD in the studied sample.

The effect of experiences in close proximity to deployment was discussed by Ikin et al (2005) as a threat (perceptions of fear or threat of attack, death, or injury despite limited exposure to direct combat, just being the Gulf zone) of developing psychiatric problems. This shows the effect of pre-deployment preparation.

Sher et al (2005) emphasizes the importance of clinical and neurobiological studies that not only may advance our understanding of the role of environmental and genetic factors in the etiology and pathogenesis of stress-related disorders, but also be useful in refining conceptions of stress-

related disorders themselves and possible approaches to the treatment of these conditions. Ruzich et al (2005) concluded that research on PTSD could:

- Minimize the large financial and personal cost of PTSD on communities and individuals.
- Finding an effective drug for PTSD could minimize the severity and occurrence of PTSD symptoms, which would alter how much compensation survivors of trauma would be entitled to receive.
- Possible association of a medical/psychosocial stressor, cognitive decline, and late-life delayed onset of PTSD symptoms in those exposed to combat-related trauma. There may also be a salient contribution from the neurobiology of PTSD and age-related neurodegeneration.
- Can we prevent the progression to delayed onset PTSD with research identifying among the factors implicated in its development: the combination of one or more of factors such as cognitive decline, psychosocial stress, or age-related neurodegeneration.

6. Conclusions:

Populations at risk (those who were subjected to trauma) after war display four categories of PTSD status based on this study: chronic, delayed onset, recovered and those who never had PTSD. In this study following a cohort of physically injured due to combat during the 1st Gulf war showed delayed onset PTSD (14.6%), chronic PTSD (15.4) recovered from PTSD (22.8%) and never had PTSD (47.2%). With chronic PTSD: cluster of symptoms severity are higher than that in those with delayed onset PTSD, severity of physical injury was not found to be related to chronicity of PTSD and more prevalence of PTSD associated symptoms such as: guilt not taking an action, survivors guilt, homicide, disappointed with others, hopelessness, memory problems. Furthermore personality subtypes, life events, anxiety, depression and other psychological symptoms e.g. hostility, phobia, OCD, somatization and cognitive problems such as psychoticism are among factors that may maintain the chronicity of PTSD. Screening a population for PTSD we found that intrusions, avoidance and arousal are PTSD cluster of symptoms more predictive of future development of PTSD.

In this sample consistent with the reports of other studies there was a lower baseline cortisol level in participants with PTSD, the levels were lower in participants with delayed onset PTSD. Furthermore trauma itself rather than PTSD may have an impact on HPA axis. In this study we found that participants with PTSD and higher cortisol level than the rest of PTSD population were having severe physical symptoms, severe Extraversion, high pulse rate, high WHR, having

GAD, MDD, somatization, OCD, hostility or a family psychiatric history. We found significant difference in mean cortisol level in participants with and high trauma score regardless of PTSD diagnosis. Furthermore the presence of comorbidity such as MDD, dysthymia or OCD did have enhancing effect on the level of cortisol in participants with PTSD. The low levels of cortisol in patients with PTSD were responsible for the continuation of the symptoms of PTSD patients. In this study the presence of family history of psychiatric disorders was associated with higher mean cortisol levels.

The thyroid functions changes in association with PTSD in this study did not reach the hyper or hypothyroid states that necessitate pharmacological intervention. All the changes are within the "normal range". Because of the sensitive nature of the thyroid gland (the hormones released), the complex factors related to PTSD symptomatology and that many factors could affect thyroid function the levels of these hormones vary from one PTSD participant to another depending on how many factor he /she has that could affect the function of this gland including factors that previously not considered like cigarette smoking and personality traits and co-morbid disorders. In general the trend of thyroid function in association with PTSD (delayed and chronic) compared to no PTSD status is lower fT3, and TSH and higher fT4 levels. It was observed that fT3 was higher in participants with delayed onset PTSD compared to participants chronic PTSD. fT3 was found in higher level (as the normal range of this hormone) in the studied sample which represents trauma survivors as 60% of the sample were in the high normal range. This was not observed for fT4 and TSH as the majority of the studied samples were having normal values of these hormones. The only significant difference comparing thyroid function PTSD and severity of trauma score was in fT3 (the higher severity of trauma score with PTSD the higher fT3 mean values). Generalized anxiety disorder, MDD, Panic attacks, cigarette smoking, and OCD in participants with PTSD caused higher mean values of thyroid hormones. Family history of psychiatric disorders has no effect on thyroid functions in PTSD participants

McCann et al (1988) proposed that psychological adaptation to war involve the development of schemas that involves safety, trust, power, self-esteem and intimacy between the person and the other persons in the environment. Further more biological, emotional, cognitive, behavioural and interpersonal factors will affect the psychological adaptation of persons to severe trauma and subsequent vulnerability to PTSD. PTSD as observed from this study involving follow up of war injures survivors for 10 years that after 10 years of the trauma still over 15% had PTSD (Chronic), and over 47% did not have PTSD. The second group could adapt to the post-war

period (up to 10 years) and did not develop the full blown picture of PTSD although we found that they have mal-adaptation in some aspects of there life in the domains that McCann has described. Furthermore the group with chronic PTSD was clear to have both psychological and biological maladaptation.

The presence of the following factors was significantly more prevalent in participants with PTSD with $p<0.001$: OCD, depression, anxiety, somatization, neuroticism and multiple physical symptoms. These participants with the previous factors are those who developed PTSD during follow up or fail to recover from PTSD developed at an earlier stage. The severity of the physical injury and the presence of family history of psychiatric disorders were not related in this study significantly for the development of PTSD.

Furthermore trauma itself rather than PTSD may have an impact on HPA axis showing low cortisol levels reported in this study in traumatized participants with and without PTSD. The cortisol level with chronic phase of PTSD is low. Moreover with delayed onset phase of PTSD the cortisol level is significantly lower than in chronic PTSD indicating attenuation of cortisol level in delayed onset PTSD.

Past history of psychiatric problems and the presence of co morbid (psychological or physical) disorders were also observed in this study to significantly predispose to PTSD as seen in the follow-up of the participants of this study. In this study secondary gain either financial or taking the sick role was not found to be having a significant role in those who developed PTSD or in those who fail to recover from PTSD. Age of the participant, marital status and education level was not significantly predictive factors for development of PTSD. Combat exposure was severe for the entire sample as the entire tested sample suffered from physical injury its role could not be evaluated in this study as a predictive factor for PTSD. .

PTSD is one form of post war psychological failure to adapt to combat war injury. Other forms of psychological maladaptation include: anxiety disorders, depression, and substance use disorders and other behavioural problems. The somatic complaints involving many body systems were another form of biological maladaptation which was more prevalent in participants with PTSD.

Severity of initial symptoms (including intrusions, avoidance or arousal) degree of initial psychological symptoms was found to significantly predict future development of PTSD in physically injured combat survivors. According to the results of this study PTSD diagnosis at one stage is not predictive of future development or chronicity of PTSD in future, but the severity of PTSD symptoms at diagnosis are significantly more predictive of future chronic PTSD. The presence of high levels of PTSD associated symptoms (e.g.: guilt not taking an action, survivors guilt, homicide, disappointed with others, hopelessness feelings, having memory problems, depressed feelings and being overwhelmed) at diagnosis were significantly more predictive of future chronic PTSD.

The minor thyroid functions alternations in chronic war related PTSD appear to be chronic, and could be detectable years after the war as this disorder changes with life-time of the survivor and the chronic nature of this disorder as seen from the results of this study assessing thyroid functions in chronic PTSD. Because of the sensitive nature of the thyroid gland (the hormones released), the complex factors related to PTSD symptomatology and that many factors could affect thyroid function the levels of these hormones vary from one PTSD participant to another depending on how many factor he /she has that could affect the function of this gland including factors that previously not considered like cigarette smoking and personality traits and co-morbid disorders.

Since the examination is a crossectional in the two phases of the study and the application of strict DSM-IV criteria for PTSD diagnosis, the role of high scores of life events in the past year (prior to the assessment), were found significantly contribute to PTSD diagnosis.

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IX. Appendices

1. General Health Questionnaire

1. Date of the interview
2. Age
3. Gender
4. Where are you living?

5. Social status: Number of wives. The wives still with the person, Still married, No of children from the first wife, Period of marriage with the first wife, Evaluation of marriage from the first wife, No of children from the second wife, Period of marriage with the second wife, Evaluation of marriage from the second wife, No of children from the third wife, Period of marriage with the third wife, Evaluation of marriage from the third wife.

No of children from the fourth wife, Period of marriage with the fourth wife, Evaluation of marriage from the fourth wife, No of children from the fifth wife, Period of marriage with the fifth wife, Evaluation of marriage from the fifth wife, No of children from the sixth wife, Period of marriage with the sixth wife, Evaluation Of Marriage From The Sixth Wife

6. No of Family Members

7. Level Of Education

8. Working before invasion: Problems with work before invasion, Working now, Problems with work now, Low work performance due to the invasion, Retired now, Retired from, Happy with the current situation, Causes of retirement, Want to work
Are you working now, what do you do, Monthly income

9. Change in living standard due to the invasion
Arguments with the family before the invasion, Violence with the family before the invasion, Financial difficulties with the family before the invasion, Substance abuse within the family before the invasion, Over-protection for the family before the invasion
Separation from the family before the invasion.

Arguments with the family after the invasion, Violence with the family after the invasion Financial difficulties with the family after the invasion, Substance abuse within the family after the invasion, Over-protection for the family after the invasion, Separation from the family after the invasion.

Arguments with friends before the invasion, Violence with friends before the invasion Financial difficulties with friends before the invasion, Substance abuse within friends before the invasion, Over-protection for friends before the invasion, Separation from friends before the invasion

Arguments with friends after the invasion, Violence with friends after the invasion Financial difficulties with friends after the invasion, Substance abuse within friends after the invasion, Over-protection for friends after the invasion, Separation from friends after the invasion

10. Worthless life, Worthless life due to war

11. Do you have psychological problems, Help for psychological problems, No of government OPD visits, No of private OPD visits inside Kuwait, Cost of private OPD visits inside Kuwait, No of private OPD visits outside Kuwait, Cost of private OPD visits outside Kuwait, No of clergy visits, Cost of clergy visits

12. Do you have psychological problems before invasion, Help for psychological problems before invasion, No of government OPD visits before invasion, No of private OPD visits inside Kuwait before invasion, Cost of private OPD visits inside Kuwait before invasion, No of private OPD visits outside Kuwait before invasion, Cost of private OPD visits outside Kuwait before invasion, No of clergy visits before invasion, Cost of clergy visits before invasion

13. Psychological medication before invasion

14. Psychological medication after invasion
Date starting psychiatric medications, Type of medications, ~~D~~do you like to take psychiatric medications

15. Hypertension and heart, Lung diseases, Gastrointestinal, Skeletal and orthopedic Dermatological, Genitourinary, Headache and fatigability, Bronchial asthma, Anemia Arthritis, Renal disorders, Diabetes, Cancer, Peptic ulcer, Liver and Gall bladder diseases Hernia, Other disorders

16. Did you ask help for the health problems, No of government OPD visits before invasion, No of private OPD visits inside Kuwait before invasion, Cost of private OPD visits inside Kuwait before invasion, No of private OPD visits outside Kuwait before invasion, Cost of private OPD visits outside Kuwait before invasion, No of clergy visits before invasion, Cost of clergy visits before invasion

No of government OPD visits during invasion, No of private OPD visits inside Kuwait during invasion, Cost of private OPD visits inside Kuwait during invasion, No of private OPD visits outside Kuwait during invasion, Cost of private OPD visits outside Kuwait during invasion, No of clergy visits during invasion, Cost of clergy visits during invasion

No of government OPD visits after invasion, No of private OPD visits inside Kuwait after invasion, Cost of private OPD visits inside Kuwait after invasion, No of private OPD visits outside Kuwait after invasion, Cost of private OPD visits outside Kuwait after invasion, No of clergy visits after invasion, Cost of clergy visits after invasion

17. Anxiety, Depression, Mania, Alcohol abuse, OCD, PTSD, Substance abuse
Other disorders

18. Current psychiatric history in the family: Anxiety, Depression, Mania, Alcohol abuse, OCD, PTSD, Substance abuse, Other disorders

19. Smoking history: Type of smoking habit, Starts smoking at age, History of stopping smoking, Period of stopping smoking, No of times stopping smoking, Last time stopped and restart again, No of cigarette per day, No of huble-bubble per day, No of pipe per day
No of cigar per day, Periods with high smoking consumption, Year of high consumption
Reasons of high consumption

20. Drinking alcohol, Period starting alcohol, Age starting alcohol, Periods with high alcohol consumption, Year of high alcohol consumption, Reasons of starting alcohol consumption, Year of starting alcohol consumption, Reasons of starting alcohol consumption,

21. Substance abuse history, Period starting substance abuse, Age starting substance abuse, Method of taking drugs, Cannabis, Hallucinogens, Other drugs, Events cause starting substance abuse, Year of starting substance abuse, Reasons caused to start substance abuse, Family problems due to starting substance abuse, Help needed to stop substance abuse,

22. First current worry
Second current worry
Third current worry
Fourth current worry
Fifth current worry

2. Trauma Questionnaire

2. A. Physical Trauma scoring

The questionnaire includes a detail analysis of the possible types of trauma adults had gone through during the invasion and occupation period of Kuwait based on our own clinical interviews, and pilot testing with volunteers. This questionnaire also had included the socio-demographic data.

The score of injury was based on Kuwait law regarding scoring disability of the injury:

1. Skin	Points		Points
Superficial scars	5	Deep scars	33
Burn % recorded as point	-	Burses,	5
2. Head and Neck			
Neurological symptoms % of disability	-	convulsions, paralysis	100
Fracture 33 point for each	33	Injuries	5
Foreign bodies- each	5	Corneal injuries	33
Visual problem % of disability	-	Tongue Direct Injury	33
Muscle weakness	50	Eating or drinking problems	100
Problem with speech % of disability	-	Fracture Jaw	33
Fracture Joint	33	Tooth loss 5 points for each	5
Loss of smelling	100	Breathing problem	100
Shrapnel's 5 points for each	5	Fracture spine	33
Hemiplegia, Hemi paresis, Incontinent	100	Hearing loss % of disability	-
3. Chest wall			
Fracture 10 points for each rib	10	Bone loss 15 points for each	15
Shrapnel 5 points for each	5	Lung tissue loss 50 points	50
Loss of function 100 points	100		
4. Spine			
Fracture 15 points for each	15	Paraplegia 100 points	100
Incontinence 100 points	100	Sexual Dysfunction 100 points	100
Paraplegia 100 points	100		
5. Abdomen			
Injury to internal organs 50 points for any	50	Dysfunction 50 points	50
Deep injury 33 points	33	Shrapnel 5 points for each	5
6. Upper and lower Limbs			
Shrapnel 5 points for each	5	Fracture 10 points for each	10
Amputation Phalanges 10 points for each	10	Amputation Shoulder 100 points	100
Amputation Wrist 50, Forearm 100	50-100		
7. Genitals			
Dysfunction productivity 100 points	100	Sexual dysfunction 100 points	100

2. B. Trauma Assessment Questionnaire before the CAPS

1. Medications were prescribed before for psychiatric problems
2. Admission for psychiatric hospital
3. Psychiatric visit were suggested
4. Clergy were consulted
5. Having superpower
6. Repeating prayers frequently
7. Taking bath more than 2 times per day
8. People plan to cause you problems
9. Nightmares before invasion
10. Sleep difficulties before invasion
11. Sexual problems before invasion
12. Alcohol or substance abuse problem before invasion
13. Temper changes rapidly before the invasion
14. Violence-aggression before invasion
15. Eating due to nervousness

Further trauma inquiry:

1. Most stressful event in the person life
2. Most stressful event for the family
3. Victim of a crime
4. Severe accident needed medical attention
5. Military-fighting participation - percentage of fighting
6. Sexual Assault
7. Which was the most stressful event?

3. Thyroid and cortisol analysis

The following as the manufacturer instructions of the kits used in the study.

Trinity biotech

*AMERLEX-MAB** FT4 Kit

CE

Intended Use
For the *in vitro* quantitative measurement of free thyroxine (FT4) in human serum and plasma (EDTA or heparin) to aid in the differential diagnosis of thyroid disease. Measurement range 0 to 130 pmol FT4/l.

Summary and Explanation of the Test
The free fraction of circulating thyroxine (T4) is considered to exert the main influence on metabolic control[1-3]. Consequently, measurement of FT4 is believed to be the most direct indicator of the thyroid status of an individual. In hypothyroidism FT4 concentration is generally depressed and in hyperthyroidism it is generally raised. FT4 measurement thus provides an aid to the differential diagnosis of thyroid disease. FT4 concentrations are independent of the concentration of thyroid hormone binding proteins[4]. Measurement of FT4 may thus be carried out on patients with elevated or reduced levels of these binding proteins[5-8] without the need for additional tests of binding capacity. In borderline cases of suspected thyroid malfunction, additional tests such as free T3, or TSH immunoassay may be necessary.

Principles of the Procedure
The *AMERLEX-MAB** FT4 Kit utilizes a direct, labelled antibody, competitive radioimmunoassay technique. FT4 present in the sample competes with a separation suspension for a limited number of binding sites on an ^{125}I-labelled mouse monoclonal anti-T4 antibody. The separation suspension, present in excess, contains magnetizable polymer particles chemically modified to act as a ligand for uncombined tracer antibody. The assay design, together with optimal reagent concentrations, ensures minimal disturbance of the T4/binding protein equilibrium in the sample. Separation of the antibody-bound fraction is effected by magnetic separation, followed by decanting of the supernatant. The amount of tracer bound is inversely proportional to the concentration of FT4 present.

Warnings and Precautions
For *In Vitro* Diagnostic Use Only

Caution - Radioactive Material
This radioactive material may be received, acquired, possessed and used only by authorized persons in clinical laboratories or hospitals and only for *in vitro* clinical or laboratory tests not involving internal or external administration of the material or the radiation therefrom to humans or animals. Its receipt, acquisition, possession, use, transfer and disposal are subject to the regulations and a general licence of Atomic Energy Agencies or of the state/national body responsible for the exercise of such regulatory authority.

Warning - Potentially Infectious Material
Human blood products provided as components of this pack have been obtained from donors who were tested individually and who were found to be negative for human immunodeficiency virus (HIV-1) antibody and hepatitis B surface antigen using approved methods (enzyme immunoassays). These components have also been tested using approved methods (enzyme immunoassay) and found to be negative for Hepatitis C Virus (HCV) antibody and HIV-2 antibody.

Care should be taken when handling material of human origin. All samples should be considered potentially infectious. No test method can offer complete assurance that hepatitis B virus, HCV, HIV 1+2 and other infectious agents are absent. Handling of samples and assay components, their use, storage and disposal should be in accordance with the procedures defined by the appropriate national biohazard safety guideline or regulation.

Warning - Contains Azide
Some components contain sodium azide (0.1% w/v). The total azide content is 110 mg (100 tests) or 440 mg (400 tests). Use copious amounts of water for disposal.

Materials Provided
1. 1/2* sets FT4 standards (freeze-dried human serum, nominal values A-F: 0, 2.5, 10, 25, 60, 130 pmol/l, exact values stated on standard value label) with Antimicrobial Agent. Reconstitution volume 1 ml.
2. 1/4* bottles *AMERLEX-MAB** separation suspension (magnetizable polymer-ligand particle suspension) in buffer with Antimicrobial Agent (55 ml).
3. 1/4* bottles tracer (^{125}I-labelled mouse monoclonal anti-T4, <370 kBq/bottle, binds >5 fmol T4/bottle) in buffer with Antimicrobial Agent (55 ml).
4. Package insert.

* 100/400 Tests.

Note: Contains bovine serum albumin and bovine gamma globulin.

Materials Required but not Provided
Precision pipettes, repeating dispenser (optional), control sera, 5 ml assay tubes and racks, plastic or metal film (to cover tubes), vortex mixer, water bath, *AMERLEX-M* separators, decanting racks, gamma scintillation counter, distilled water.

Reagent Preparation and Storage
Do not use reagents beyond the expiration date stated on the package label. Store unopened reagents at 2-8 °C. Do not freeze.

Standards: reconstitute with 1 ml distilled water. Store at 2-8 °C for up to 4 weeks.

All other reagents are supplied ready for use, store at 2-8 °C after opening.

Sample Collection, Preparation and Storage
Serum or plasma (EDTA or heparin) samples may be used. Store samples at 2-8 °C for up to 7 days or at -20 °C for up to 3 weeks. Avoid repeated freezing and thawing.

Quality Control and Procedural Notes
1. Reagents from the same lot number may be combined in a clean glass vessel. Samples and reagents should be brought to 18-28 °C and thoroughly mixed (avoiding excessive foaming) before use. All reagents should be dispensed without interruption. The dispensing times of the *AMERLEX-MAB** separation suspension and tracer should not exceed 10 and 5 minutes respectively. Dispense the tracer immediately after completing dispensing of the separation suspension.
2. Run a separate standard curve, in duplicate, for each assay. Controls and samples should be assayed in duplicate. Good laboratory practice requires that controls be run to verify the performance of the assay. Radioassay controls with high medium and low levels of FT4 should be run.
3. Ensure all tubes contact the separator base during separation. Do not remove rack from separator base when decanting and draining tubes. Do not reinvert drained tubes once they have been turned upright.

Test Protocol

Procedure
1. Assemble and label assay tubes.
2. Pipette 50 µl standard, control or sample into appropriate tubes.
3. Dispense 500 µl *AMERLEX-MAB** separation suspension into all tubes.
4. Dispense 500 µl tracer into tubes.
5. Vortex, cover and incubate at 37 °C for 30 minutes.
6. Attach the rack to the separator base, leave for 15 minutes. Decant and drain for 5 minutes with blotting.
7. Count tubes so as to accumulate at least 2 000 counts in the F standard tubes.

Results
Plot standard curve, either manually or using an RIA curve fit programme. Results may be calculated using logit-log or linear plotting.

Linear-linear Plotting
Plot standard counts (corrected for background if required) against concentration on linear graph paper. Draw the best curve through the mean of duplicate points, rejecting grossly aberrant counts. Read the concentration of the unknowns from the standard curve.

Logit-log Plotting
Correct counts for background (if measured) then calculate percentage bound (%B/Bo) relative to the zero standard mean (Bo) for each standard and unknown (B) i.e. (B/Bo) x 100. Plot %B/Bo against standard concentration on logit-log graph paper. Draw the best straight line through the mean of duplicate points, rejecting grossly aberrant counts. Read the concentration of the unknowns from the standard curve.

Table 1: Sample Calculation
(expressed in pmol/l)

Tube Number	Sample	Standard Conc.	Counts/min X1	Counts/min X2	Mean FT4 Conc.
1-2	Totals		110092	113596	
3-4	Std A	0	53013.2	52046.4	
5-6	Std B	2.5	41266.9	40607.6	
7-8	Std C	10.0	23573.1	22617.5	
9-10	Std D	25.0	11737.2	11478.7	
11-12	Std E	60.0	5239.6	5006.6	
13-14	Std F	130	2389.6	2300.9	
15-16	U1†		44681.1	44875.1	1.6
17-18	U2		17497.1	16710.4	14.8
19-20	U3		6917.8	7023.3	45.5

† Unknown

Limitations of the Procedure

1. The results obtained from this or any other diagnostic kit should be used and interpreted only in the context of an overall clinical picture.

2. Lipemic, haemolyzed and icteric samples may be used up to levels of 33.9 mmol/l triolein, 5 g/l haemoglobin and 1.7 mmol/l bilirubin. Do not use turbid samples.

3. Heat treated samples give elevated FT4 values due to protein denaturation and disturbance of the FT4/T4 equilibrium.

4. Heterophilic antibodies in serum or plasma samples may cause interference in immunoassays[9]. These antibodies may be present in blood samples from individuals regularly exposed to animals or who have been treated with animal serum products. Results which are inconsistent with clinical observations indicate the need for additional testing.

Expected Values

It is recommended that each laboratory establish its own reference interval. As a guide, a normal reference interval of 11 to 24 pmol FT4/l with a mean of 16.1 pmol/l (95% confidence interval using a log transform) was obtained from 483 patients of euthyroid status, not on thyroid treatment. No differences in FT4 concentrations were observed between males and females and there was no correlation with age. Of 87 hyperthyroid patients tested, 95.4% had FT4 concentrations >24 pmol/l. Of 59 hypothyroid patients tested, 93.2% had FT4 concentrations <11 pmol/l.

A study of apparently euthyroid pregnant women showed a progressive reduction in FT4 concentration as pregnancy advances. The means and ranges (95% confidence intervals) for the first, second and third trimesters were 15.4 pmol/l (11.6 to 19.2 pmol/l, 42 samples), 12.8 pmol/l (9.3 to 16.3 pmol/l, 44 samples) and 11.6 pmol/l (8 to 15.2 pmol/l, 43 samples) respectively. In patients with non-thyroidal illness FT4 concentrations were normal or occasionally depressed. For example, the mean FT4 concentration in 32 apparently euthyroid patients with renal failure was 15.3 pmol/l, with a range of 9.9 to 24.3 pmol/l.

Performance Characteristics

1. Calibration

The assay was calibrated indirectly against equilibrium dialysis. A correlation between the *AMERLEX-MAB** FT4 Kit and an FDA cleared assay has been obtained by measuring a panel of 623 patient samples from a variety of clinical categories:

*AMERLEX-MAB** FT4 Kit = 1.05 x FDA cleared assay - 0.23 (pmol/l), with a correlation coefficient of 0.96.

FT4 concentrations are quoted in units of pmol/l or ng/dl. Conversion of units may be made using the formula:

Result in ng FT4/dl = result in pmol FT4/l x 0.078

2. Reproducibility

Four freeze-dried control sera were assayed in 10 replicates to determine within-assay reproducibility. To determine between-assay reproducibility 16 assays were performed by 6 operators using different reagent batches. The data presented are representative of the performance found over the shelf life of the product.

Table 2: Reproducibility
(expressed in pmol/l)

Within-assay Mean	Within-assay CV(%)	Between-assay Mean	Between-assay CV(%)
5.6	6.5	5.3	7.5
14.2	3.7	13.9	5.9
17.8	3.8	17.8	6.2
46.8	3.7	47.6	5.0

3. Sensitivity

Sensitivity is defined as the concentration 2 standard deviations from the zero standard when 20 replicates are determined. The sensitivity of the *AMERLEX-MAB** Free T4 Kit is typically 0.6 pmol/l.

4. Specificity

The percentage cross-reactivity on a molar basis was 1.2% for L-3,3',5-triiodothyronine, 15.6% for L-3,3',5'-triiodothyronine (reverse T3), >100% for D-thyroxine and <0.02% for mefenamic acid. Cross-reactivity of <0.01% was exhibited for 3,5-diiodo-L-tyrosine, 3-iodo-L-tyrosine, diphenylhydantoin, phenylbutazone, sodium salicylate and o-acetylsalicylic acid, fenclofenac, methimazole, 6n-propyl-2-thiouracil and frusemide.

Note: Bio-Rad controls, Catalogue number 370, are commercially available to use as controls for this product. Please contact Trinity Biotech Technical Services at (353) 1 276 9800, for expected values

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RISK AND SAFETY

Sodium azide

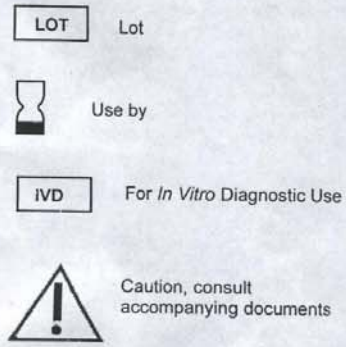
R22: Harmful if swallowed.
R32: Contact with acids liberates very toxic gas.
S36: Wear suitable protective clothing.

Xn

Prepared in accordance with requirements for EEC label.

EINECS 247-852-1

Key Guide to Symbols



IM.5051 (100 Tests)
IM.5054 (400 Tests)

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242-008 11/03

Coat-A-Count® TSH IRMA

English

Intended Use: Coat-A-Count TSH IRMA is an immunoradiometric assay designed for the quantitative measurement of thyroid stimulating hormone (thyrotropin, TSH) in serum. It is intended strictly for *in vitro* diagnostic use as an aid in the assessment of thyroid status.

Catalog Numbers: **IKTS1** (100 tubes), **IKTS2** (200 tubes), **IKTS5** (500 tubes), **IKTSX** (1000 tubes).

The 100-tube kit contains less than 20 microcuries (740 kilobecquerels) of radioactive ^{125}I-polyclonal anti-TSH; the 200-tube kit contains less than 40 microcuries (1,480 kilobecquerels); the 500-tube kit contains less more than 100 microcuries (3,700 kilobecquerels); and the 1,000-tube kit contains less than 200 microcuries (7,400 kilobecquerels).

Summary and Explanation of the Test

Thyroid stimulating hormone (thyrotropin, TSH) is a pituitary hormone which, through its action on the thyroid gland, plays a major role in maintaining normal circulating levels of the iodothyronines, T4 and T3. TSH is controlled by negative feedback from circulating T4 and T3, and by the hypothalamic hormone TRH (thyrotropin releasing hormone).

In primary hypothyroidism, where there is impaired production of thyroid hormones, the TSH level is typically highly elevated. In secondary or tertiary hypothyroidism, on the other hand, where thyroid hormone production is low as a consequence of pituitary or hypothalamic lesions, the TSH level is usually low. In hyperthyroidism, the TSH level is typically suppressed to subnormal levels. Less often, this condition may result from hyperstimulation of the thyroid, due to hypothalamic or pituitary lesions, in which case the TSH level is usually increased.

Measurement of circulating TSH has been used as a primary test for differential diagnosis of hypothyroidism[19] and as an aid in monitoring the adequacy of thyroid hormone replacement therapy.[18]

Research studies have found that the apparently healthy patients with TSH >2.0 µIU/mL have increased risk to develop thyroid diseases in the next 20 years. It has been suggested that it is likely that the upper limit of the serum TSH euthyroid reference range will be reduced to 2.5 µIU/mL because >95% of rigorously screened normal euthyroid volunteers have serum TSH values between 0.4 and 2.5 µIU/mL.[22]

Principle of the Procedure

Coat-A-Count TSH IRMA is a solid-phase immunoradiometric assay based on monoclonal and polyclonal anti-TSH antibodies: one ^{125}I-labeled anti-TSH polyclonal antibody in liquid phase, and monoclonal anti-TSH antibodies immobilized to the wall of a polystyrene tube. In the procedure:

TSH is captured between monoclonal anti-TSH antibodies immobilized on the inside surface of the polystyrene tube and the radiolabeled polyclonal anti-TSH tracer.

Unbound ^{125}I-labeled anti-TSH antibody is removed by decanting the reaction mixture and washing the tube; this reduces nonspecific binding to a very low level, and ensures excellent low-end precision.

The TSH concentration is directly proportional to the radioactivity present in the tube after the wash step. The radioactivity is counted using a gamma counter, after which the concentration of TSH in the patient sample is obtained by comparing the patient counts-per-minute with those obtained for the set of calibrators provided.

Reagents to Pipet: 1

Total Incubation Time: 2 Hours

Total Counts at Iodination: approximately 200,000 cpm.

Warnings and Precautions

For *in vitro* diagnostic use.

Reagents: Store at 2–8°C in a refrigerator designated for incoming radioactive materials. Dispose of in accordance with applicable laws.

Do not use reagents beyond their expiration dates.

Some components supplied in this kit may contain human source material and/or other potentially hazardous ingredients which necessitate certain precautions.

Follow universal precautions, and handle all components as if capable of transmitting infectious agents. Source materials derived from human blood were tested and found nonreactive for syphilis; for antibodies to HIV 1 and 2; for hepatitis B surface antigen; and for antibodies to hepatitis C.

Sodium azide, at concentrations less than 0.1 g/dL, has been added as a preservative. On disposal, flush with large volumes of water to prevent the buildup of potentially explosive metal azides in lead and copper plumbing.

Water: Use distilled or deionized water.

Radioactivity
A copy of any radioisotope license certificate (Specific or General) issued to a US customer must be on file with Diagnostic Products Corporation before kits or components containing radioactive material can be shipped. These radioactive materials may be acquired by any customer with the appropriate Specific license. Under a General license these radioactive materials may be acquired only by physicians, veterinarians in the practice of veterinary medicine, clinical laboratories and hospitals — and strictly for *in vitro* clinical or laboratory tests not involving external or internal administration of the radioactive material or its radiation to human beings or other animals. Its acquisition, receipt, storage, use, transfer and disposal are all subject to the regulations and a (General or Specific) license of the U.S. Nuclear Regulatory Commission or a State with which the NRC has entered into an agreement for the exercise of regulatory control.

Handle radioactive materials according to the requirements of your General or Specific license. To minimize exposure to radiation, the user should adhere to guidelines set forth in the National Bureau of Standards publication on the *Safe Handling of Radioactive Materials* (Handbook No. 92, issued March 9, 1964) and in subsequent publications issued by State and Federal authorities.

Wipe up spills promptly and decontaminate affected surfaces. Avoid generation of aerosols. Dispose of solid radioactive waste according to license requirements. General licensees (holders of NRC Form 483) may dispose of solid radioactive waste as nonradioactive waste, after removing labeling. Specific licensees (NRC Form 313) should refer to Title 10, Code of Federal Regulations, Part 20. Licensees in Agreement States should refer to the appropriate regulations of their own state. General licensees may dispose of liquid radioactive waste of the type contained in this product through a laboratory sink drain. Licensees must remove or deface labels from empty containers of radioactive materials before disposal of solid waste. Specific licensees may dispose of small quantities of liquid radioactive waste of the type used in this product through a laboratory sink drain. Refer to the appropriate regulations applicable to your laboratory.

Materials Supplied – Initial Preparation

TSH Ab-Coated Tubes (ITS1)
Polystyrene tubes coated with murine monoclonal antibodies to TSH and packaged in zip-lock bags. Store refrigerated and protected from moisture, carefully resealing the bags after opening. Stable at 2–8°C for one year from the date of manufacture.
IKTS1: 100 tubes. **IKTS2:** 200 tubes. **IKTS5:** 500 tubes. **IKTSX:** 1000 tubes.

^{125}I TSH Ab (ITS2)
Iodinated anti-TSH goat polyclonal antibody, with preservative. The reagent is supplied in liquid form, ready to use. Each vial contains 5.5 mL. Stable at 2–8°C for 30 days after opening, or until the expiration date marked on the label. Color: red.
IKTS1: 2 vials. **IKTS2:** 4 vials. **IKTS5:** 10 vials. **IKTSX:** 20 vials.

TSH Calibrators (TSI3–9,X)
Eight vials, labeled A through H, of lyophilized TSH calibrators in an equine